A COMPARATIVE STUDY ON NEUROCOGNITION AND AFFECTIVE TEMPERAMENT IN FIRST-DEGREE RELATIVES OF BIPOLAR DISORDER PATIENTS

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CERTIFICATE

This is to certify that the dissertation title, **"A COMPARATIVE STUDY ON NEUROCOGNITION AND AFFECTIVE TEMPERAMENT IN FIRST-DEGREE RELATIVES OF BIPOLAR DISORDER PATIENTS"** submitted by **Dr. L. THENMOZHI**, in partial fulfillment for the award of the MD degree in Psychiatry by The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is a bonafide record of the work done by her in the Institute of Mental Health, Madras Medical College during the academic years 2010 - 2013.

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DECLARATION

I, **Dr. L. THENMOZHI,** solemnly declare that the dissertation titled, **"A COMPARATIVE STUDY ON NEUROCOGNITION AND AFFECTIVE TEMPERAMENT IN FIRST-DEGREE RELATIVES OF BIPOLAR DISORDER PATIENTS"** has been prepared by me, under the guidance and supervision of **Dr. R. JEYAPRAKASH** M.D., D.P.M., Professor of Psychiatry, Madras Medical College. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.D degree **Branch – XVIII (Psychiatry)** to be held in April 2013.

Place : Chennai **Dr. L. THENMOZHI**

Date :

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CONTENTS

INTRODUCTION

Psychiatric disorders are a product of multiple biological and environmental factors, resulting in a heterogenous presentation. Though the knowledge about bipolar disorder dates back to ancient times, there is much to be explored about the nature and etiology of the illness. Bipolar disorder is one of the most disabling illnesses in psychiatric classification, which has a cyclical course. Studies have demonstrated the substantial heritability of the illness in twin studies and 10-20 fold increase in risk of bipolar disorder in first-degree relatives of bipolar probands when compared to general population.

There is functional impairment even in patients who are in remission. There is a need to conduct more research into the biological etiology specific to bipolar disorder. Genetics in psychiatry, its prime goal is to find how genes influence psychiatric illnesses, the pathway from genotype to phenotype. The familial nature of major psychiatric illnesses is shown by family, twin and adoption studies. Identifying genes relied upon linkage analysis or candidate gene-based association analysis. Although BPD has been shown to be highly heritable, the search for its genetic loci has been impeded by its complexity. The term ‘genetics’ was given by William Bateson in the year 1902. In 1909, Danish botanist Wilhelm Johanssen gave the concepts, ‘genotype’ and ‘phenotype’ and introduced

the term ‘gene’. Genotype, which is the genetic constitution, can be measured by molecular biology techniques like, polymerase chain reaction and DNA sequencing. Phenotype is the visible characteristics of an organism, which is the product of genotype and the environmental influences. Other factors influencing the expression of phenotypes include epigenetic. With the introduction of genome wide association studies (GWAS), there has been a great impact in genetic studies. The aim of GWAS is to capture all common genetic variations across the genome and to relate this variation to disease risk. It surveys the whole genome with up to one million or more genetic markers.

The first step is to identify validated susceptible variants and the second step is to define the functional effects of these variants. Delineating the effects of risk genes on specific domains of brain function can provide insight into the mechanisms by which, these genes produce the illness.

Despite all advances in genetic studies, psychiatry had only little success in definitely identifying culprit genes or gene regions. Looking for the reason of this is the inherent complexity of psychiatric disorders.

“The brain is the most complex of all organs”

To fill this gap between the genotype and phenotype, the concept of ‘endophenotype’ was adopted.

The importance of research in endophenotypes is of many fold, such that it paves the way for improved understanding of the neurobiology and genetics of psychopathology, establishing biological underpinnings for diagnosis and classification,. Cognitive impairment and affective temperament are established endophenotypic markers of bipolar disorder. Assessing the level of impairment in them may help to ascertain whether cognitive impairment and affective temperament could be considered as endophenotypes of BPD. Neurocognitive impairment and dominance of certain affective temperament are proven in bipolar disorder patients during illness phase, in their euthymic phase and in their first-degree relatives. There are only fewer studies in Indian setup in establishing the neurocognitive dysfunction and affective temperament as the endophenotypes of bipolar disorder, especially in relatives of bipolar disorder probands. So my study aims at assessing the neurocognitive impairment and the specific temperament in the first-degree relatives of bipolar probands when compared to normal unrelated controls and to study if there is any association between the cognitive impairment and affective temperament in the relative group, and between cognitive impairment, affective temperament of relative group and the illness characters of bipolar probands.

REVIEW OF LITERATURE

Gottesman et al. and Shields et al. (2003) described "endophenotypes as internal phenotypes discoverable by microscopic examination or biochemical test". The term was adapted by John et al. and Lewis et al. in their research paper published in 1966. Endophenotypes may help in identifying the aberrant genes in the hypothesized polygenic systems offering vulnerability to disorders.

Feasible methods for analysis of endophenotypes are biochemical, neurophysiological, endocrinological, neuroanatomical, cognitive and neuropsychological. Synonymous terms for endophenotypes are "intermediate phenotype", "biological marker", "subclinical trait", "vulnerability marker" (Leboyer et al., Bellivier et al. 1998).

Gottesman et al. (2003) gives criteria for an endophenotype as follows.

1. The endophenotype is associated with illness in the population.
2. The endophenotype is heritable.
3. The endophenotype is primarily state-independent.
4. Within families, endophenotype and illness co-segregate.

5. The endophenotype found in the affected family members is also found in the non-affected family members, at a higher rate than in the general population.

The search for the candidate endophenotypes have been described in the literature on several psychiatry disorders including schizophrenia, mood disorders, alzheimer's diseases, attention deficit hyperactivity disorder and even personality disorders.

ILLUSTRATED CLASSES OF ENDOPHENOTYPES RELEVANT TO PSYCHIATRIC DISEASES

Alzheimer's disease

Neurocognitive measures of memory performance

Reduced brain electrophysiological EEG activity

Attention-deficit/hyperactivity disorder

Structural brain imaging: reduced right prefrontal gray matter and left occipital gray and white matter

Functional brain imaging: prefrontal cortex and cerebellum deficits

Neuropsychological measures of inhibition and processing speed

Autism

Neuropsychological measures of social cognition

Anxiety disorder

Functional brain imaging: greater amygdala and insula activation to emotional faces

Temperament traits: negative affectivity/neuroticism, positive affectivity, behavioral inhibition, effortful control

Neuropsychological measures of attentional bias toward stimuli relating to threats and negative emotions

Obsessive-compulsive disorder

Structure brain-imaging: structural variation in brain systems related to motor inhibitory control; white matter abnormalities in parietal and frontal regions

Neuropsychological and functional MRI measures of cognitive flexibility and motor inhibition

Schizophrenia

Structural brain imaging: smaller intracranial volumes, frontal and temporal gray matter reductions, hippocampal volume reduction

Neurophysiology: auditory P300, sensory-gating, eye-movement deficits

Functional brain imaging: dorsolateral prefrontal cortex dysfunction

Neuropsychological measures of attention, executive function, working memory, processing speed

Clinical features: thought disorder, schizotypal personality disorder

Substance-related disorders

Neurophysiology: resting EEG, visual P300 event-related potential

Major depression

Neuropsychological measures of cognitive

function Temperament trait: neuroticism

Clinical characteristics: number of episodes, duration of episodes, high levels of impairment, recurrent thoughts of death or suicide

Bipolar disorder

Structural brain imaging: alterations in gray and white matter

Neurophysiology: auditory P300; P50 sensory gating

Neuropsychological measures of executive function, verbal learning and memory, facial-emotion processing, deficits in ventral prefrontal cortex– related inhibitory processes, attention

Temperament traits: affective temperament

ADVANTAGES IN STUDYING ENDOPHENOTYPES

Endophenotypes help to characterize how risk genes are related to neurobiological and neurophysiological phenotypes that underlie psychiatric disorders; to shift the focus of research from gene discovery to functional characterization.

Endophenotype mapping of susceptibility genes for psychiatric disorders may help in identifying the specific domains of brain function, influenced by relevant risk gene variants of disorders.

They help us to find out whether a disease risk gene variant is related to single or multiple cognitive processes that underlie psychiatric disorders.

They help to throw a light on the neurobiological mechanisms or neural circuits by which the risk genes exert their effects.

Endophenotypes could inform the evolution of psychiatric nosology. They help in classifying patients on the basis of similar neuropsychological and cognitive functional deficit profiles into homogenous bio-cognitive subtypes across diagnostic categories. Thus testing the validity of clinical classification of psychiatric disorders.

NEUROCOGNITION

Cognition denotes “a relatively high level of processing specific information such as thinking, memory, motivation, perception, language and skilled movements”.

Campbell’s psychiatric dictionary says, among the specific functions that may be assessed in determining the adequacy and intactness of cognition are orientation, new learning ability, problem solving, abstract thinking, reasoning and judgment, ability to retain and recall events, mathematical ability and symbol manipulation, control over primitive reactions and behavior, comprehension and language use, attention, perception and praxis.

Deficits in cognition may result in the inability to

1. Pay attention.
2. Process information quickly.
3. Remember and recall information.
4. Respond to information quickly.
5. Think critically, plan, organize and solve problems.
6. Initiate speech.

Recently, cognitive psychology has evolved as a prime area of research in a number of psychiatric disorders. Cognitive research has begun to unlock various issues of psychiatric disorders, for example biological underpinnings, explaining the psychopathology and related aspects like the course of illness, the outcome and treatment strategies.

NEUROCOGNITIVE IMPAIRMENT IN PSYCHIATRIC DISORDERS

The following table illustrates the cognitive impairment established in various psychiatric disorders.

Schizophrenia :Working memory, verbal episodic memory, attention,executive function, old learning, vocabulary, visual perceptual skills

Mood disorders : Attention, executive function, verbal memory

Obsessive compulsive disorder : visuospatial, visuoconstructional, non verbal memory (encoding and retrieval), executive function

Somatoform disorder : Semantic memory, verbal episodic memory and visuospatial tasks

Borderline personality disorder :executive function Attention- vigilance, verbal learning, verbal memory,

Substance abuse : Attention, encoding new information, cognitive flexibility, problem solving

HERITABILTY OF COGNITIVE ABILITIES

Heritability is defined as *"the extent to which the variation in a particular phenotype is accounted for by genetic variation"*. It is ascertained that IQ scores predict neuropsychological performance in a wide spectrum of cognitive abilities. It is shown that the heritability estimates of standardized IQ tests, to be 50-80% (Bouchared et al.,1998; Wright et al.,2001; Bartels et al.,2002).

Despite the evidence for substantial heritability of intelligence, the search for specific genes that affect performance on tests of intelligence has not been fruitful. The reason for this may be because intelligence is not a unitary construct, but involves a wide range of discrete cognitive processes. So, in order to find out the genetic influences of basic mental abilities, behavioral geneticists investigated measures of specific neurocognitive domains. **Such studies demonstrated that cognitive domains that are strongly influenced by genetics are attention, executive functioning, speed of processing, working memory and declarative memory.**

Cornblatt et al. (1988) found the heritability value of sustained attention by using continuous performance tests to be 0.49. Similarly 41% of heritability is given by Myles-Worsley and Coom (1997) for selective attention.

Anokhin et al(2003) showed the heritability of about 37-46% for cognitive flexibility in Wisconsin card sorting test.

The heritability estimate of working memory shown in various studies by Finkle and McGue, (1993), Ando et al. (2001), Lucino et al. (2001) is 30-60%.

NEUROCOGNITION IN BIPOLAR DISORDER

Literature and studies on the neurocognition in bipolar disorder demonstrate a number of cognitive impairments in patients with bipolar disorder when compared to healthy controls.

It has been long recognized that mania is associated with changes in cognition and affect (Kraepelin, 1921; Bunney and Hartman, 1965).

The most consistent findings are deficits in the areas of attention, verbal memory and executive function (Quraishi and Frangou, 2002; Malhi, Ivanovski, Szekers and Olley, 2004).

Simonsen et al. in his report demonstrates that one-fourth of patients with bipolar I disorder have a clinically significant range of cognitive impairment.

Similar findings were given by Savard et al. (1980) who administered the Halstead-Reitan category test to acutely depressed unipolar and bipolar patients, naïve of medications and showed that patients in bipolar group made significantly more errors.

Marked impairment in test of learning and verbal fluency was demonstrated by Wolfe et al. (1987) in a group of patients with bipolar disorder compared to patients with unipolar depression.

Taylor and Abrams (1986) showed nearly half of the patients with mania had moderate or severe global cognitive impairment in tests of attention, visuospatial function and memory.

A study by Henry et al.(1971) reported that there is impairment in serial word list learning in manic phase. He also demonstrated that the reduction in performance was directly related to increase in severity of illness.

Cognitive impairment in manic phase of bipolar disorder was also proven by Murphy et al.(1999). In tests of pattern and spatial recognition memory and delayed visual recognition.

" The memory structure of manic patients compared to normal controls, where loose, over inclusive and idiosyncratic which led to difficulties in filtering the environmental stimuli and a tendency to over generalize" (Andreason and Powers, 1974). Also studies show impairment in executive functioning in manic patients by using tests of attentional set-shifting (Morice,1990; Clark et al.,2000), planning ability (Murphy et al.,1999) and decision making(Clark et al.,2000;Murphy et al.,2001).

NEUROCOGNITION IN EUTHYMIC PHASE OF BIPOLAR DISORDER

It was assumed that bipolar disorder patients regain intact cognition after their recovery from an acute episode, but this has been disproved by recent studies, which show there is neuropsychological dysfunction in euthymic phase of bipolar disorder as well. Malhi et al., 2005 studied 12 bipolar patients in their euthymic phase comparing with 12 normal controls and concluded that bipolar patients show cognitive impairment in their euthymic phase.

Van Gorp et al. (1998) who employed rigorous definition of euthymia in 13 bipolar disorder patients and a control sample of 22 that matched on general intellectual ability and years of education, found **executive and verbal memory dysfunction in euthymic phase of bipolar patients.**

Ferrier et al. (1999) in a study sample of 41 bipolar patients in euthymic state and 20 healthy controls, reported residual impairment of executive function in euthymic bipolar patients, after controlling for age and premorbid intelligence.

Rubinsztein et al. (2000) found asymptomatic patients with bipolar disorder , in remission for at least 4 months, to show deficits on tests of visuospatial recognition memory, response latency in tests of executive functioning.

Sapin et al., assessed 20 bipolar patients who had remained euthymic for a month and were 2 week drug free, and found that they had impairment in facial recognition compared with normal controls.

Cavanagh et al.,2002 (20 euthymic bipolar patients and 20 normal controls)and Clark et al., 2002 (30 euthymic bipolar patients and 30 healthy controls) showed neurocognitive deficits on tasks of verbal learning and memory in euthymic bipolar patients.

Thompson et al. (2000) reported deficits in both verbal learning and executive function in prospectively verified euthymic patients with bipolar disorder (n=63) whose mood was no different from that of controls (n=63) in standard clinical ratings.

Similar findings were demonstrated by Zubieta et al. (2001) on measures of verbal learning, executive function and motor coordination which were impaired in bipolar patients (n=15) in their euthymic state when compared to 15 normal controls.

A study by Taj M. and Padmavathy et al. (2005) from Schizophrenia research centre, Chennai, showed impairment in domains of attention, memory and executive functioning in euthymic bipolar patients, in their study comparing 30 euthymic bipolar patients and 30 controls.

NEUROCOGNITIVE DYSFUNCTION AND BIPOLAR ILLNESS CO-SEGREGATION IN FAMILIES

Fewer studies were available to asses this association that cognitive dysfunction and bipolar disorder co-segregate in families.

Altshuler et al. (2004) showed that executive dysfunction and verbal memory deficits in their bipolar group with a bimodal distribution, suggesting the presence of two sub groups, one with impairment and another with normal neurocognitive function.

This is also replicated in a study by Thompson et al. (2005), who found significant deficits in the performance on a wide range of neurocognitive tasks in a sample of euthymic patients, but only a minority of patients appeared to account for this patient- control group performance differences.

So the association between bipolar illness and cognitive performance and the co-segregation of neuropsychological dysfunction with the illness in families is not clearly established.

NEUROCOGNITION IN UNAFFECTED RELATIVES OF RELATIVES OF BIPOLAR DISORDER PATIENTS

Early studies of cognition in relatives of bipolar disorder patients used tests of general intelligence. Later more specific cognitive tasks were studied.

Gourovitch et al. (1999) studied the neurocognition in affected and non-affected monozygotic twins(7) and 15 controls. The results were memory deficits in both twin groups evidenced by the Wechsler memory scale and the California verbal learning test.

Though cognitive deficits of various domains have been shown in unaffected first-degree relatives of bipolar patients, **the most consistent were deficits in working memory and executive function.**

In comparing the 20 unaffected siblings of bipolar and schizophrenia patients to 20 normal controls , Keri and Colleagues (2001) found deficits in delayed verbal memory in both sibling groups.

In a study conducted by Zalla (2004) comparing the executive function of bipolar and schizophrenia patients and their unaffected first-degree relatives (33) with normal controls (20), the results were bipolar disorder patients and their relatives poorly performed on Stroop color-word interference test than controls. This proves increased susceptibility to interference and deficits in response inhibition.

Ferrier and colleagues (2004) studied the neuropsychological functioning in 17 unaffected first-degree relatives of bipolar patients and 17 matched unrelated controls using standard neuropsychological battery assessing psychomotor functioning, executive function and declarative memory. They showed unaffected first-degree relatives of bipolar patients had significant impairment in visual declarative memory and executive control.

Bora and colleagues (2007) demonstrated deficits in verbal working memory and executive functions in studying 34 unaffected first-degree relatives of bipolar patients compared to 25 normal controls, when they studied five cognitive domains of executive function (Wisconsin card sorting test, trail making test, Stroop color word test), verbal learning (Rey auditory verbal learning test), working memory (auditory consonant trigrams, backward digit span test, letter – number sequencing test), sustained attention (Conner's continuous performance test II) and psychomotor speed (trail making test A (TMT A), Conner's continuous performance test II response time, digit span).

Similar results were shown by Antilla et al. (2007) with unaffected first-degree relatives of bipolar patients(n= 40) displaying deficits in psychomotor performance and executive functioning compared to healthy controls (n=55).

Research into various domains of executive functioning in unaffected first-degree relatives of bipolar patients reveal impairment in set shifting and response-inhibition. Clark et al. (2005) showed attentional set shifting is impaired in 27 unaffected first-degree relatives of bipolar patients compared to 46 normal controls, using 'The intradimensional /extradimensional shift task' developed from Wisconsin card sorting test, indicating dorsal prefrontal executive function impairment.

Whereas, Frangou et al. (2005) in his study comparing 15 unaffected relatives of bipolar patients and 43 normal controls showed evidence for deficits in tasks of ventral but not dorsal prefrontal executive function in the relative group. They proved this by displaying impairment in response inhibition by using Wisconsin card sorting test (WCST)and the Hayling sentence completion task.

Frantom et al. (2008) studied the neurocognitive function of 19 bipolar I disorder, 19 unaffected first-degree relatives and 19 normal controls, in the domains of visuo-spatial constructional abilities, executive function, visual learning and memory, and motor speed. And concluded that there is impairment in the following domains in unaffected first-degree relatives of bipolar patients compared to normal controls – visuo-spatial constructional domain (block design and judgment of line orientation),visual learning and memory (Biber trials 1-5, Wechsler memory scale III, Faces I, Rey 3 minute delay), executive function.(WCST, perseverative errors).

Two recent meta-analyses were conducted in this area. One by Arts et al. (2007) regarding the cognitive functioning in euthymic bipolar patients and their unaffected first-degree relatives showed **executive function and verbal memory as candidate endophenotypes of bipolar disorder**. Another meta-analysis by Bora et al. (2009) concluded **response inhibition to be the most prominent endophenotypes of bipolar disorder** showing the ventral prefrontal dysfunction.

There are three Indian studies regarding the neurocognitive endophenotypes of bipolar disorder.

Trivedi et al. (2008) compared neurocognitive function in 10 unaffected first-degree relatives of bipolar patients with 10 matched controls using computer based neurocognitive tests of spatial working memory, continuous performance test, WCST. Study revealed significant impairment in tests of executive function and vigilance in the relative group than control group, suggesting these domains could be potential endophenotypic markers of bipolar disorder.

Kulkarni et al. (2010) demonstrated deficits in verbal learning and memory, and executive function as endophenotypes of bipolar disorders, where the unaffected first-degree relatives of bipolar patients (30) performed poorly on the following tests compared to unrelated healthy controls (30) : Tower of London test, the Rey's auditory verbal learning test and the Rey's complex figure test.

Pattanayak and his colleagues (2012) studied neurocognition using Trail making test A and B, Stroop color word test, N-back verbal memory test, PGI memory scale in 20 healthy first-degree relatives of bipolar disorder patients and 20 unrelated normal controls. Study showed poor performance of unaffected first-degree relatives of bipolar disorder patients in set-shifting task of Trail making test B (TMT-B) , implying dorsal prefrontal executive dysfunction.

AFFECTIVE TEMPERAMENT

The word "Temperament", is derived from "*temperare*" meaning 'confusion'. *"It is the attitude and behaviors on structural, genetic and biological basis"* (Goodwin and Jamison).

"Temperament is a person's predisposition towards certain patterns of reactivity, mood and sensitivity. And this remains stable over time and is heritable". (Goldsmith et al.) The association between affective illness and temperament can be traced to ancient Greece and Rome…

"Those prone to the disease(bipolar disorder) are such as are naturally passionate, irritable, of active habits, of an easy disposition, joyous, puerile : like wise those whose disposition inclines to the opposite condition, namely, such as are sluggish, sorrowful, slow to learn, but patient in labour, and who when they learn anything soon forget it; those likewise are more prone to melancholy who have formerly been in a mad condition" [Aretaeus of Cappadocia (AD 30-90)].

"There are certain temperaments which may be regarded as rudiments of manic- depressive. They may throughout the whole of life exist as peculiar forms of psychic of personality without further development; but they may also become the point of departure for a morbid process which develops under peculiar conditions and runs its course in isolated attacks".(Kraepelin 1921)

Kraepelin (1921) saw depression and mania as manifestations of an identical underlying pathology, which is genetic in etiology and expressed in multiple forms. He gave four basic affective dispositions- depressive, hyperthymic, cyclothymic and irritable, predisposing to manic- depressive illness. The modern concept of affective temperament was given by Akiskal, who described five principal affective temperaments- depressive, hyperthymic, cyclothymic, irritable and anxious.

HERITABILITY OF TEMPARAMENT

Literature shows that personality traits are at least partly influenced by genetic factors.

Twin studies have demonstrated the heritability estimates for the Five factor model personality traits of between 40% and 60 % and similar results for the Temperament and character inventory four dimensions of temperament.

The behavioral genetics data are congruent with molecular genetic work which facilitated the identification of genetic variants that appear to influence specific personality traits. On this basis, the association between anxiety-related traits with polymorphisms of serotonin transporter (SERT) gene and between novelty seeking related traits with polymorphism of dopamine four receptor (DRD4) gene was shown by Lesch et al. (1996) and Ebstein et al. (1996) .

AFFECTIVE TEMPERAMENTS IN BIPOLAR DISORDER

The association between affective temperament and bipolar disorder has been stated in the previous quotes from literature. According to Kraepelin (1913), it was cyclothymic temperament which was predominantly associated with a predisposition for classical form of the illness.

Von Zessen et al. and Possl et al. (1990) studied the incidence of affective temperament in the following patient groups : 10 unipolar mania, 11 bipolar I, 11 bipolar II, 10 endogenous unipolar depression. Of this melancholic temperament was present in 75% of the unipolar depression group and manic temperament was predominant in the unipolar mania (80%) and bipolar I (67%) groups.

In a study by Cassano et al.(1992), of 35 bipolar I and 94 bipolar II patients, about 40% of the bipolar I and 20% of the bipolar II groups presented with depressive temperament and 25% of both groups presented with hyperthymic temperament.

Evans et al. (2005) showed higher scores of depressive and cyclothymic temperament in a study of 155 bipolar I and bipolar II patients, and 63 unrelated normal controls using the temperament Evaluation of Memphis, Pisa, Paris and San Diego –Auto questionnaire (TEMPS-A).

Cyclothymic temperament was presented in 88% of bipolar II disorder patients in a study by Hantouche et al. (1998) studying 99 bipolar II patients , similar results were replicated by Benazzi et al. and Akiskal et al. studying 62 bipolar II patients and 59 unipolar depressive patients. (2005)

Henry et al. (1999) argued that bipolar disorder was predisposed by presence of hyperthymic temperament.

PERSONALITY TRAITS IN EUTHYMIC BIPOLAR DISORDER PATIENTS

Not just the personality traits / temperament is associated during the illness period but it is reported that bipolar disorder patients appear to be more unstable emotionally even in their euthymic phase.

Higher scores of depressive, cyclothymic and anxious temperament was found in a sample of 30 remitted bipolar patients compared to healthy controls (Matsumoto et al.2005).

Barbara et al. (2010) studied affective temperament and impulsivity using TEMPS-A and Barratt Impulsivity Scale (BIS-11) in three groups: 45 euthymic bipolar patients, 1096 students and 45 controls. The results were more prominent depressive, cyclothymic, irritable and anxious temperament and impulsivity in bipolar disorder group.

This shows that affective temperament personality traits are state independent.

Another way of demonstrating this association is by analyzing the premorbid personality features of individuals who then develops bipolar disorder

Angst et al. and Clayton et al. (1986) in their follow up study of 591 individuals , showed that emotional lability was a significant risk factor for bipolar disorder.

High scores of TCI cooperativeness and self-transcendence was shown to be associated with unipolar depression patients who developed bipolar II disorder later (Akiskal et al.1995)

TEMPARAMENT AND BIPOLAR DISORDER CO-SERGREGATION IN FAMILIES

This is association is not clearly evident as it is not sure that only one subtype of bipolar spectrum illness in the family.

Literature search shows that this co-segregation of temperament and bipolar disorder in families with the available knowledge cannot be evaluated or classified.

AFFECTIVE TEMPARAMENT IN UNAFFECTED FAMILY MEMBERS OF BIPOLAR DISORDER PATIENTS

The final criterion to say that affective temperament could be an endophenotype marker of bipolar disorder is that it must be present in unaffected family members of bipolar patients. Many studies demonstrated this adding to the support in favor of temperament to be considered an endophenotype of bipolar disorder.

Akiskal et al. (1985) studied the affective temperament of offsprings and siblings of bipolar probands and he showed that out of 68 subjects, 12 met the criteria for dysthymia. In another study, he showed the cyclothymia was the most consistent temperament dominated in the biological relatives of bipolar patients.

Similar results that cyclothymic temperament score was higher in unaffected relatives of bipolar patients compared to normal uncertain controls were demonstrated Klein et al.(1986) in comparing 37 first-degree relatives of bipolar disorder patients with 22 normal controls, and Maier et al.(1995) comparing 167 first-degree relatives of bipolar patients, 228 first-degree relatives of unipolar patients with 223 healthy unrelated controls.

Chiaroni et al. (2005)studied the temperament in 3 groups : 100 normal subjects with no family history of affective disorder, 37 symptom - free individuals with a family history of unipolar depression, 40 symptom -

free individuals with family history of bipolar disorder. He demonstrated that cyclothymic temperament was highest in bipolar family history groups, intermediate in the unipolar depression group and least in controls.

Weissman et al. (1984) in his study of affective temperament concluded that, cyclothymic temperament and hyperthymic temperament aggregated in relatives of bipolar I patients (n=203).

Dominance of hyperthymic temperament also shown by kesebir et al. (2005) in his study comparing 100 patients with bipolar disorder and their 219 unaffected fisrt-degree relatives to unrelated normal controls, using TEMPS-A.

Mauro et al. and colleagues (2004) studied affective temperament comparing three groups, 52 healthy relatives bipolar patients, 23 bipolar patients who were in remission and normal controls. They used TEMPS-A short version. They concluded that, healthy relatives bipolar patients exhibited significant cyclothymic instability in mood, self-confidence, interest, energy and sleep, and anxiety proneness compared to normal controls. they also proposed that this could be used as endophenotype marker for bipolar disorder.

Gustavo et al. (2007) in his study comparing affective temperament in 114 unaffected first-degree relatives of bipolar patients and 115 matched normal controls with no family history of affective illness, using TEMPS-

A, showed cyclothymic and anxious subscales were significantly higher in unaffected first-degree relatives of bipolar patients than controls. This signifies the use of affective temperament as endophenotypes of bipolar disorder.

With this background regarding endophenotype of bipolar disorder, my study aims at assessing the neurocognition and affective temperament in first-degree relatives of bipolar disorder patients in comparison with unrelated healthy controls. As the neurocognition and affective temperament are demonstrated as endophenotypes of bipolar disorder, assessing the correlation between the two is needed. So this study also aims at studying the correlation between the neurocognition and affective temperament in first-degree relatives of bipolar disorder patients.

AIMS AND OBJECTIVES

AIM

To study the neurocognition and affective temperament in first-degree relatives of patients with bipolar I disorder in comparison with normal controls.

OBJECTIVES

1. To assess and compare the working memory and executive function of first-degree relatives of bipolar I disorder patients and normal controls.
2. To assess and compare the affective temperament of first-degree relatives of bipolar I disorder patients and normal controls.
3. To identify the relationship between working memory, executive function and affective temperament of first-degree relatives of bipolar I disorder patients.
4. To identify the relationship between working memory, executive function & affective temperament in first-degree relatives of patients with bipolar I disorder and the clinical characteristics of bipolar I disorder patients.

NULL HYPOTHESIS

1. There is no difference in performance, of the study and control groups, in tests of working memory.

2. There is no difference in performance, of the study and control groups , in tests of executive function.

3. There is no difference in the affective temperaments of the study and control groups.

4. There is no relationship between working memory, executive function & affective temperament of first-degree relatives of patients with bipolar I disorder.

5. There is no relationship between working memory, executive function & affective temperament of first-degree relatives of patients with bipolar I disorder and the clinical characteristics of bipolar I disorder patients.

MATERIALS AND METHOD

The study is a cross sectional observational case control study, conducted at the Institute of Mental Health, Chennai. Consecutive patients attending both outpatient department and inpatient department were screened for diagnosis of bipolar I disorder using MINI- plus structured clinical interview for DSM IV. 30 first-degree relatives of the bipolar I disorder patients, fulfilling the selection criteria were chosen as study group.

Selection criteria

Inclusion criteria:

1. First-degree relatives (parents, siblings & children) of patients diagnosed to have bipolar I disorder.
2. Subjects between 18 – 50 years of age.
3. Formal education up to 8^{th} std.
4. Giving informed consent.

Exclusion criteria:

1. Mental retardation
2. H/o any psychiatric illness.
3. H/o concurrent neurological illness or systemic illness known to impair cognition.

4. H/o head injury with loss of consciousness.
5. H/o any substance dependence.
6. H/o benzodiazepine or any other medication use known to impair cognition in the last 1 month period.

TOOLS EMPLOYED

1. MINI-plus structure clinical interview for diagnosing bipolar I disorder, based on DSM IV criteria.

2. Proforma for socio demographic data of study (cases) and control group.

3. Proforma for clinical characteristics of bipolar patients related to study group which includes age of onset, duration of illness, severity of illness, presence of psychotic symptoms, no. of hospitalizations, no. of suicide attempts, presence of substance use.

4. Raven's progressive matrices

The standard test for measuring IQ. The scoring was in terms of percentile. A percentile score of 25^{th} shows average intelligence. Scores more than 25 as above average and highly intellect according to percentile scores. Subject who scored 25^{th} or more than 25^{th} percentile were taken.

5. Tests for working memory

Working memory is capacity to hold and manipulate information for ongoing processes. The three components of working memory are verbal

working memory, visuo-spatial working memory and a central executive. Working memory is externally and internally guided.

a. Verbal working memory

The N back tests used for verbal working memory, are the 1 back and 2 back version of the N back test devised by Smith and jonides, 1999 from the NIMHANS neuropsychology battery, 2004. This test the externally guided working memory. In this test 30 randomly ordered consonants common to multiple Indian languages are presented auditorily at the rate of 1 per second. Of these 9 consonants are repeated. The repeated consonants are randomly chosen. In the 1 back test the subject responds whenever a consonant is repeated consecutively. Whereas in the 2 back test the subject respond whenever a consonant is repeated after an intervening consonant. The number of hits and errors are scored. Errors include the number of omission and commission errors. The total number of errors is taken for computation.

b. Visual working memory

For testing visual working memory N back test with 1 back version, from the NIMHANS neuropsychology battery, 2004 is used. It consists of 36 cards. A black dot is placed randomly along the circle imagined to be on the card, in each card. The dimension and location of the imaginary circle remains constant in all cards. Each card is presented individually to

the subjects. The subject is asked to respond whenever the location of the dot repeated consecutively. The number of hits and errors is scored. The total number of errors is taken for calculation.

6. Test for executive function

a. Wisconsin card sorting test

Wisconsin card sorting test developed by Milnar in 1963 is used to test the set-shifting ability. This test examines concept formation, abstract reasoning and the ability to shift cognitive strategies in response to changing environments. It consists of 64 tests cards and 4 stimulus cards. Each card is a square of dimensions 8cms by 8cms. The stimuli vary in three attributes : color(red, green, yellow, blue), form(triangle, star, cross, circle) and number(1,2,3,4). Of these four stimulus card the first card consist of one red triangle, the second card consist of 2 green stars, the third card consist of 3 yellow crosses and the fourth card consist of 4 blue circles.

The four stimulus cards are placed in front of the subject, with one red triangle placed on the left had side of the subject. Next to it is the card with two green stars, followed by the card with 3 yellow crosses and on the extreme right the card with 4 blue circles. The deck of 64 cards is arranged according to the sequence of presentation given in the test manual and placed to the left side of the subject. The subject is asked to study the cards

and match each successive card from the pack to one of the four stimulus card. The subject is told only whether each response is right or wrong and never about the correct sorting principal. Each time the subject places a card according to the sorting principal it is scored starting from 1 and continued serially for consecutive correct responses. After 10 consecutive correct responses, the examiner changes the concept without the knowledge of the subject. The first matching principal is by color then form and finally number. This sequence is repeated.

The scoring is done for the number of trials administered, total number of correct responses, total number of errors, percent errors, perseverative responses, percent perseverative responses, perseverative errors , percent perseverative errors, non perseverative errors, percent non perseverative errors, conceptual level responses, percent conceptual responses, number of categories completed.

b. Stroop test

This test measures the response inhibition ability. Three cards which has 20 rows and 5 columns of either color names or symbol is presented. First card has color names printed in black color, second card has x symbol printed in different colors. And last card has color names blue, green , and red printed in different colors (e.g. red printed in green color)

First card is presented to the subject and asked to read the color words along the column. Then, second card is given and the number of X symbols read is noted. Third card given and the subject has to read the color in which the color names are printed and not the color names. The time taken to read each card (t1, t2, t3) and the number of errors made is noted. The Stroop effect is calculated as : t3-(t1+t2 / 2).

c. Trail making test B

Trail Making Test has two parts A and B. Each part consists of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the subject is asked to draw lines connecting the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); the subject is asked to connect the circles in an ascending order, but the additional task is alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc.). The subject is instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time taken to complete the trail is noted. If the subject makes an error, it is pointed out immediately and correction allowed.

7. The Temperament Evaluation of Memphis, Pisa, Paris and San Diego – Auto questionnaire, short version (TEMPS-A) for affective temperament.

The TEMPS- A short version developed by Hagop S. Akiskal in 2003 is from his auto questionnaire long version, which was from his interview version. The short version of TEMPS-A is a validated scale for assessing the affective temperament, which it does in five subscales : cyclothymic, depressive, irritable, hyperthymic and anxious. The cyclothymic subscale has 12 questions, depressive 8 , irritable 8, hyperthymic 8, anxious 3 questions under them. Answer is 'yes' or 'no' for every question. The scoring is done by computing the number of yes responses under each subscale for every subject.

Ethical committee approval obtained from Madras Medical College.

Fifty two patients diagnosed to have bipolar I disorder by clinical examination were administered MINI PLUS structured clinical interview for DSM IV diagnosis of bipolar I disorder for diagnostic confirmation. Their first degree relatives (parents, siblings, children) were screened for selection criteria. 30 relatives were included in the study. They were excluded because, 4 had a of major depressive episode in their past, 3 had history of seizure disorder and were on antiepileptic medications, 9 had history of alcohol dependence, 1 had history of cannabis dependence, 5 had taken alcohol within one month period.

30 age and education matched normal controls were taken from general population with the same exclusion criterion. In addition with no h/o any psychiatric illness in the family.

(4 were excluded, - 2 had family history of seizure disorder, 1 family history of mental retardation, 1 had family history of bipolar disorder)

Both the study and control groups were employed MINI-plus to exclude the presence of any psychiatric illness at the start of the study.

After explaining the complete nature of the study, consent was obtained from both groups. The socio demographic data of the study & control group, and the clinical characteristics of the bipolar I disorder patients were collected.

All the tests were preferably administered in two settings in consecutive days.

DATA ANALYSIS AND RESULTS

STATISTICAL ANALYSIS:

- Comparison of socio demographic data of study and control groups: Chi square test
- Comparison of working memory, executive function and affective temperament, of study and control groups: Mann-whitney U test
- To assess the relation between working memory, executive function and affective temperament of first-degree relatives of patients with bipolar I disorder : Spearman's correlation
- To assess the relation between working memory, executive function and affective temperament of first-degree relatives of patients with bipolar I disorder and the clinical characteristics of bipolar I disorder patients: Spearman's correlation

RESULTS

The study is a case control study, cases defined as first-degree relatives of bipolar I disorder and controls as healthy unrelated subjects.

A. Socio-demographic data of cases and controls

With respect to study population (cases), 15 were less than 35 years of age and 15 more than 35 years. Sex distribution was also equal among cases, 15 male and 15 female. And 18 (60%) had a secondary education, while 12 (40%) had a degree.

With respect to control group), 18 (60%) were less than 35 years of age and 12 (40%) more than 35 years. Sex distribution among controls, 17 (56.7%) male and 13 (43.3%) female. And distribution in education was equal, 15 had a secondary education, while 15 had a degree

Table 1 : socio-demographic data

Sociodemographic data	Cases(n=30)		Controls(n=30)	
	Number	**Percent**	**Number**	**Percent**
Age : less than35 More than 35	15 15	50 50	18 12	60 40
Sex : male Female	15 15	50 50	17 13	56.7 43.3
Education :secondary Degree	18 12	60 40	15 15	50 50
Occupation : unemployed Unskilled Semiskilled Skilled	8 5 12 5	26.7 16.7 40.0 16.7	9 4 9 8	30 13.3 30.0 26.7
Marital status : married Unmarried	22 8	73.3 26.7	16 14	53.3 46.7
Domicile : rural Urban	13 17	43.3 56.7	5 25	16.7 83.3
SES :low Middle	5 25	16.7 83.3	2 28	6.7 93.3
Religion : Hinduism Christianity Islam	22 5 3	73.3 16.7 10.0	28 2 0	93.3 6.7
Relationship to patient: parent Sibling Children	 11 9 10	 36.7 30.0 33.3	 -	 -

B. Comparison of socio-demographic data

Table 2 : Comparison of socio-demographic data of study and controls

Sociodemographic data	Cases(n=30)	Controls(n=30)	$\chi 2$
Age : less than35 More than 35	15 15	18 12	0.475
Sex : male Female	15 15	17 13	0.605
Education :secondary Degree	18 12	15 15	0.436
Occupation : unemployed Unskilled Semiskilled Skilled	8 5 12 5	9 4 9 8	0.731
Marital status : married Unmarried	22 8	16 14	0.108
SES :low Middle	5 25	2 28	0.228
Religion : Hinduism Christianity Islam	22 5 3	28 2 0	0.082

No significance seen in chi square testing

Comparison of socio-demographic data of cases and controls shows no significant difference. Hence the two groups are comparable with respect to age, sex distribution, education, occupation, socio-economic status.

C. Illness characteristics of bipolar probands

The below table 3 shows the details regarding the illness characteristics of bipolar probands.

Table : 3 illness characteristics of bipolar probands

	N	Mean	Std. Deviation
ONSET AGE(yrs)	30	24.40	7.509
DURATION OF ILLNESS(yrs)	30	9.00	7.755
NO. MANIC EPISODES	30	2.90	1.918
NO. DEPRESSIVE EPISODES	30	.53	.776
NO. MIXED EPISODES	30	.17	.461
ILLNESS SEVERITY	30	2.40	2.044
PSYCHOTIS SYMPTOMS(yes)	30	1.07	.254
NO OF HOSPITALISATIONS	30	3.37	2.236
NO OF SUICIDE ATTEMPTS	30	.40	.932
SUBSTANCE USE(yes)	30	1.73	.450

The mean age of onset of bipolar disorder is 24.40 years and the mean duration of illness is 9 years. The severity of illness is calculated by dividing the duration of illness by the sum of manic, depressive and mixed episodes.

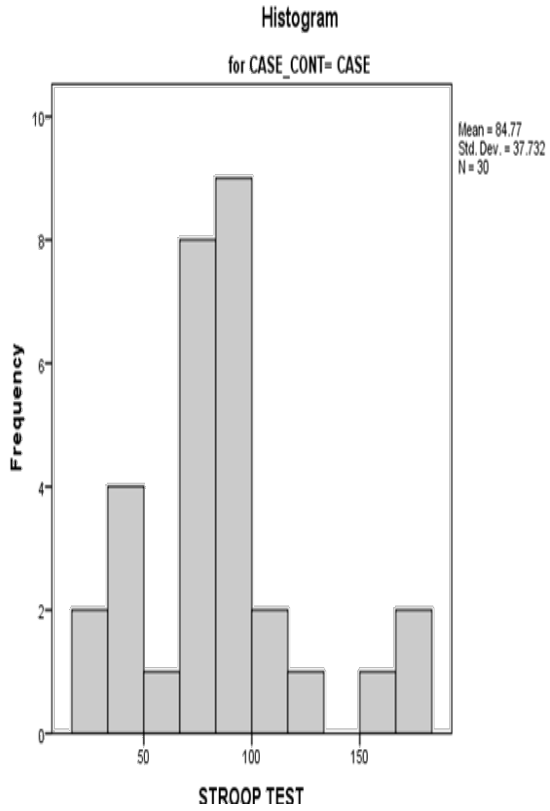
D. Assessment of normal distribution of data

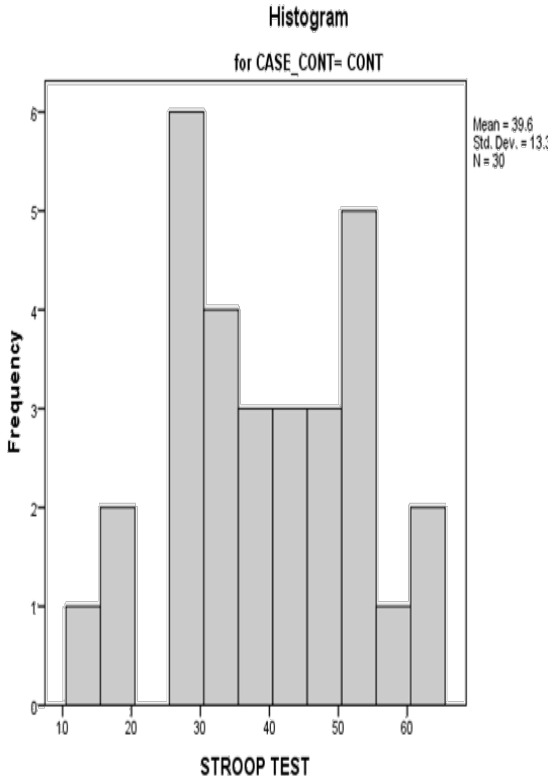
Shapiro-Wilk test is used to assess the normal distribution of data.

Table 4 : Assessing normality of data for cases and controls

Tests of Normality

	CASE_CONT	Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig.	Statistic	Df	Sig.
STROOP TEST	CASE	.153	30	.071	.927	30	.041
	CONT	.115	30	.200*	.974	30	.647

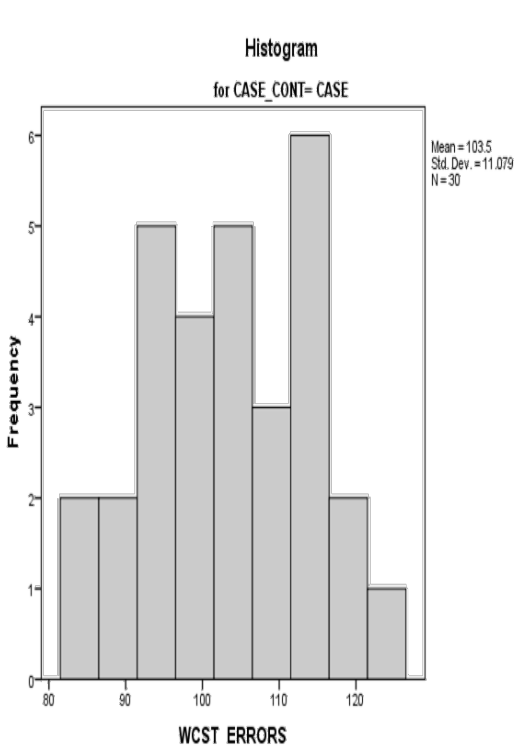


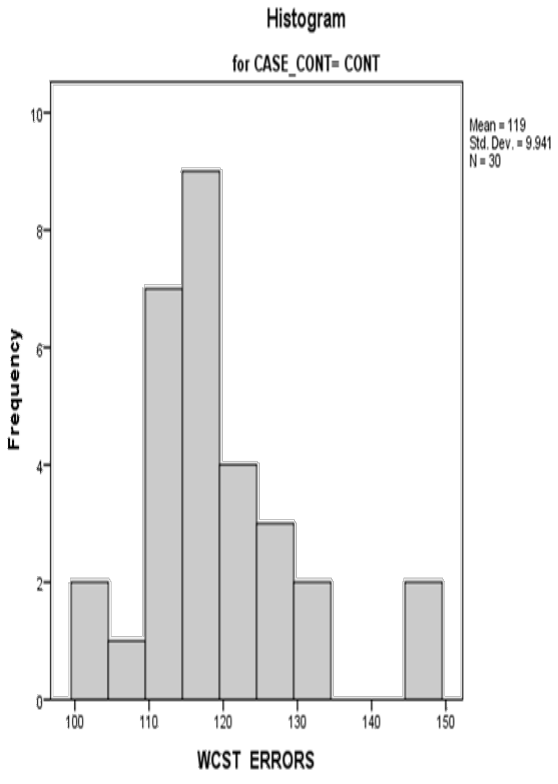


Shapiro-Wilk test, which is a standard test for assessing the normal distribution of data. The above table 4 gives the normality testing for cases and controls for Stroop test. The result s significant (0.041) for cases but not significant for controls (0.647). this means the data falls under normal distribution curve for cases but not controls, as depicted pictorially in the histogram.

Tests of Normality

CASE_CONT		Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	Df	Sig.
WCST ERRORS	CASE	.128	30	.200*	.962	30	.353
	CONT	.173	30	.022	.903	30	.010



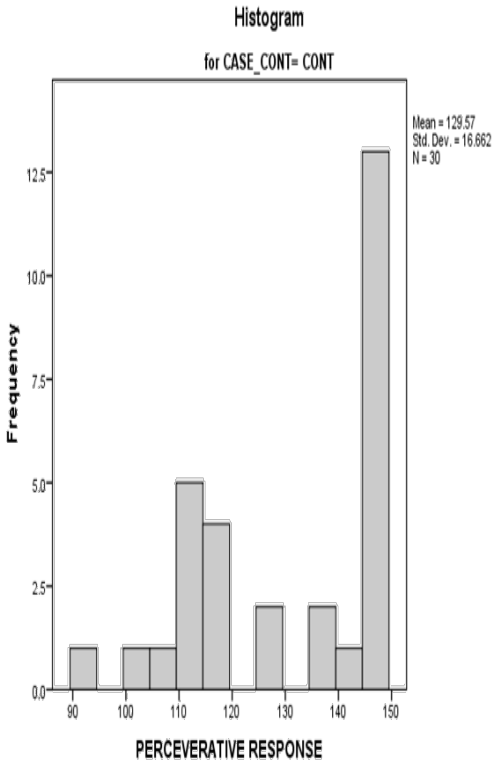


Similarly for Wisconsin card sorting test score of errors (WCST), Shapiro-Wilk test shows non-normal distribution for cases but normal distribution for controls. Also depicted in the histogram.

The next data for perseverative response shows non-normal distribution for cases.

Tests of Normality

	CASE_ CONT	Kolmogorov-Smirnov			Shapiro-Wilk		
		Statistic	Df	Sig.	Statistic	df	Sig.
PERCEVERATIVE RESPONSE	CASE	.165	30	.037	.942	30	.105
	CONT	.256	30	.000	.824	30	.000



The results were similar for rest of the variables also. Hence non parametric tests are used for comparison of variables between cases and controls.

E. Comparison of neuropsychological scores between cases(study group) and controls

A total of 6 neuropsychological tests (N back test for verbal and visual working memory, trail making test - B, Stroop test, Wisconsin card sorting test) were administered to cases and controls, yielding 16 scores. For the tests of working memory verbal N back 1 and 2, visual N back 1, the total number of errors were taken. Lower the scores better the performance, higher the scores, poorer the performance. For trail making test the time taken to complete is scored in seconds. Higher the score poorer the performance. For Stroop test, Stroop effect is calculated, higher the score poorer the performance. The standard scores from Wisconsin card sorting test manual are entered for each parameter. Higher the score better the performance.

The Wilcoxon – Mann-whitney U test (non parametric test) is used for comparison of neuropsychological test scores of cases and controls.

I. Tests for verbal working memory

Table 5 : comparison of verbal working memory between cases and controls

VERBAL WORKING MEMORY								
TESTS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
N BACK 1	1.47	1.592	.10	.305	165.000	630.000	-4.798	.000**
N BACK 2	4.70	2.037	2.07	.740	72.500	537.500	-5.725	.000**

*P<0.05 ; **P<0.01

For N back test 1, cases group made more errors (mean 1.47, SD 1.592) compared to controls (mean 0.10, SD 0.305). The Mann-whitney U score, Wilcoxon W and Z scores comparing two groups are 165.000 (U), 630.000 (W), -4.798 (Z) respectively. And the test scores are statistically significant at $p < 0.01$

For N back 2, in cases, mean score was 4.70, SD 2.037 and in controls mean is 2.07, SD 0.740; Mann-whitney U 72.500 , Wilcoxon W 537.500 and Z -5.725 and shows statistical significance at $p<0.01$ [table 5]

II. Test for visual working memory

Table 6 : comparison of visual working memory between cases and controls

VISUAL WORKING MEMORY								
TESTS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
N BACK 1	4.20	2.413	.77	.898	67.500	532.500	-5.749	.000**

*P<0.05 ; **P<0.01

In N back test 1, cases made more number of errors (mean 4.20, SD 2.413) when compared to controls (mean 0.77, SD 0.898) The Mann-whitney U score is 67.500, Wilcoxon W is 532.500 and Z score is -5.749 comparing two groups . The total number of errors was more in cases than in controls. And the test scores are statistically significant at $p < 0.01$ [table 6]

III. Test for executive functioning – Trail making test B

Table 7 : comparison of executive functioning – Trail making test B between cases and controls

EXECUTIVE FUNCTION								
TESTS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
TMT B (sec)	151.43	82.227	69.73	14.906	98.000	563.000	-5.209	.000**

*P<0.05 ; **P<0.01

TMT B – Trail Making Test B

Trail making test B tests the set-shifting ability of a subject. In this, cases took longer time to complete the task (mean 151.43, SD 82.227) when compared to the control group (mean 69.73, SD 14.906). On comparing the performance of two groups, there was significant difference with $p<0.01$; the Mann-whitney U score is 98.000 , Wilcoxon W is 563.000 and Z score is -5.209 [table 7]

IV. Test for executive functioning – Stroop test

Table 8 : comparison of executive functioning – Stroop test between cases and controls

EXECUTIVE FUNCTION- STROOP TEST								
TESTS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
STROOP EFFECT (sec)	84.77	37.732	39.60	13.343	107.500	572.500	-5.065	.000**

*P<0.05 ; **P<0.01

Stroop test is used to test the response inhibition of executive functioning. It scores the time taken to complete each card and the number of errors made in each. The Stroop effect calculated using the time factor, shows cases (mean 84.77, SD 37.732)took more time to complete the task compared to the control group (mean 39.60, SD 13.343). Though the errors were not used in computation of Stroop effect, cases made more errors compared to the controls in all 3 cards. The scores in the Mann-whitney U is 107.500 , Wilcoxon W 572.500 and Z score is -5.065 ; the difference in their performance was statistically significant p<0.01 [table 8]

V. Test for executive functioning – Wisconsin card sorting test

Wisconsin card sorting test (WCST) is the gold standard test for executive function testing. The raw scores for each parameter were noted and their corresponding standard scores entered from test manual. The overall performance was better in control group compared to cases who made more number of errors (total and perseverative) and perseverative responses. So the standardized scores were low in cases compared to controls.

Table 9 : comparison of executive functioning – Wisconsin card sorting test between cases and controls

EXECUTIVE FUNCTION- WCST								
TEST PARAMETERS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
E	103.50	11.079	119.00	9.941	127.500	592.500	-4.558	.000**
%E	87.93	15.722	112.73	12.077	86.000	551.000	-5.208	.000**
PR	106.87	20.436	129.57	16.662	113.500	491.500	-2.798	.005**
%PR	88.63	22.570	119.93	22.014	133.500	539.500	-3.574	.000**

*P<0.05 ; **P<0.01

E – Errors ; %E – Percent Errors ; PR – Perseverative Response ; %PR – Percent Perseverative Response

The scores on comparison of WCST errors are, Mann-whitney U 127.500, Wilcoxon W 592.500 and Z score is -4.558 ; The scores on comparison of WCST percent errors are, Mann-whitney U 86.000 , Wilcoxon W 551.000 and Z score -5.208 ; similarly for WCST perseverative response the scores are, Mann-whitney U 113.500 , Wilcoxon W 491.500 and Z score is -2.798; for percent perseverative response Mann-whitney U 133.500 , Wilcoxon W 539.500 and Z score is -3.574

All these tests show statistically significance difference between the two groups $p<0.01$ [table 9]

The scores on comparison of WCST perseverative errors are, Mann-whitney U 166.500, Wilcoxon W 631.500 and Z score -4.233. The scores for WCST percent perseverative errors are, Mann-whitney U 122.500, Wilcoxon W 587.500 and Z score -4.849. Scores for WCST non perseverative errors are, Mann-whitney U 207.000, Wilcoxon W 672.000 and Z score -3.601; for WCST percent non perseverative errors , Mann-whitney U 189.000, Wilcoxon W 654.000 and Z score -3.866; all the test scores were statistically significant at $p<0.01$ [table 10]

Table 10 : comparison of executive functioning –

Wisconsin card sorting test between cases and controls

EXECUTIVE FUNCTION- WCST								
TEST PARAMETERS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
PE	106.53	19.380	129.83	15.563	166.500	631.500	-4.233	.000**
%PE	86.90	21.114	118.87	19.650	122.500	587.500	-4.849	.000**
NPE	104.33	13.679	116.03	11.279	207.000	672.000	-3.601	.000**
%NPE	94.13	16.309	110.23	11.717	189.000	654.000	-3.866	.000**

*P<0.05 ; **P<0.01

PE – Perseverative Errors ; %PE – Percent Perseverative Errors ; NPE – Non perseverative Errors ; %NPE – Percent Non Perseverative Errors

Table 11 : comparison of executive functioning –

Wisconsin card sorting test between cases and controls

EXECUTIVE FUNCTION- WCST								
TEST PARAMETERS	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
CLR	34.30	14.077	50.87	4.740	116.500	581.500	-4.947	.000**
%CLR	85.80	16.818	110.17	11.695	105.000	570.000	-5.107	.000**
CC	2.43	1.431	4.47	.900	116.000	581.000	-5.150	.000**

*P<0.05 ; **P<0.01

CLR – Conceptual Level Response ; %CLR – Percent Conceptual Level Response ; CC – Categories Completed

Table 11 gives the Wilcox – Mann-whitney U test for the remaining parameters of WCST. The comparison scores are : conceptual level response Mann-whitney U 116.500 , Wilcoxon W 581.500 , Z score -4.947 ; percent conceptual level response Mann-whitney U 105.000 , Wilcoxon W 570.000 , Z score -5.107 ; categories completed, Mann-whitney U 116.000 , Wilcoxon W 581.000 , Z score -5.150. all the test were significant p<0.01

F. Comparison of affective temperament measures of cases and controls

The total score of 'yes' response for each subscale in the Temperament Evaluation of Memphis, Pisa, Paris and San Diego – Auto questionnaire, short version (TEMPS-A) is calculated for cases and controls, compared using Wilcoxon – Mann-Whitney U test.

Table 12 : comparison of affective temperament between cases and controls

AFFECTIVE TEMPERAMENT								
SUBTYPES	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
CT	2.20	2.657	1.13	1.943	287.500	752.500	-2.526	.012*
DT	.90	1.583	.60	.894	434.000	899.000	-.269	.788
IT	1.27	1.437	1.13	1.502	403.000	868.000	-.738	.460

*P<0.05 ; **P<0.01

CT – Cyclothymic Temperament ; DT – Depressive Temperament ; IT – Irritable Temperament

The mean score for cyclothymic temperament in cases is 2.20 and controls is 1.13; Mann-Whitney U score is 287.500, Wilcoxon W 752.500, Z score -2.526; for depressive temperament the mean score in cases is 0.90 and controls is 0.60; Mann-Whitney U score 434.000, Wilcoxon W 899.000, Z score -.269; for irritable temperament mean score in cases is

1.27 and controls is 1.13; Mann-Whitney U score 403.000 , Wilcoxon W 868.000, Z score -.738 [table 12]

Table 13 : comparison of affective temperament between cases and controls

AFFECTIVE TEMPERAMENT								
SUBTYPES	CASES (n=30)		CONTROLS (n=30)		MANN-WHITNEY U	WILCOXON W	Z	SIGNIFICANT 2 TAILED
	MEAN	SD	MEAN	SD				
HT	3.67	2.309	1.77	2.582	238.000	703.000	-3.217	.001**
AT	.47	.507	.23	.504	337.000	802.000	-2.038	.042*

*P<0.05 ; **P<0.01

HT – Hyperthymic Temperament ; AT – Anxious Temperament

The mean score for hyperthymic temperament in cases is 3.67 and controls is 1.77; Mann-Whitney U score 238.000, Wilcoxon W 703.000, Z score -3.217; for anxious temperament the mean score in cases is 0.47 and controls is 0.23; Mann-Whitney U score 337.000 , Wilcoxon W 802.000 , Z score -2.038 [table 13]

The statistically significant difference is noted in cyclothymic ($p<0.05$), hyperthymic ($p<0.01$), and anxious temperament ($p<0.05$)

G. Correlation between neuropsychological tests and affective temperament in cases

The following tables shows correlation between neuropsychological tests and affective temperament, between neuropsychological tests, affective temperament and illness characteristics of bipolar probands of the study (cases) group. The statistical test used to measure this correlation is the spearman's correlation test, computing the spearman's rho.

Table 14 : working memory, TMT B Vs affective temperament in cases

			CT	DT	IT	HT	AT
Spearman's rho	VERBAL WM N BACK1	Correlation Coefficient	.267	-.373*	-.029	.031	.088
		Sig. (2-tailed)	.153	.042	.880	.870	.642
	VERBAL WM N BACK 2	Correlation Coefficient	.424*	-.033	.368*	-.072	.466**
		Sig. (2-tailed)	.019	.863	.045	.707	.009
	VISUAL WM N BACK 1	Correlation Coefficient	.398*	-.077	.309	-.271	.196
		Sig. (2-tailed)	.029	.686	.096	.148	.299
	TMT B	Correlation Coefficient	.298	-.048	.155	-.007	.178
		Sig. (2-tailed)	.109	.800	.414	.973	.348

*p <0.05 **p <0.01

CT – Cyclothymic Temperament ; DT – Depressive Temperament ; IT – Irritable Temperament ; HT – Hyperthymic Temperament ; AT – Anxious Temperament

Table 14 shows the correlation between tests of working memory verbal and visual, trail making test with temperament subscales.

Spearman's correlation shows that there is significant correlation between the scores of verbal working memory N back 1 and depressive temperament of the cases. It also shows significant correlation between verbal working memory N back 2 performance and cyclothymic , irritable and anxious temperament. There was no significant correlation found between TMT B and any of the temperament subscales.

Table 15 shows correlation between Stroop test performance, Wisconsin card sorting test scores and the temperament. There was significant correlation between Stroop test and the hyperthymic temperament.

The Wisconsin card sorting scores of total number of errors, percent errors, perseverative response, percent perseverative response had no significant correlation with the temperament subscales as shown in table 15.

Table 15 : Stroop test, WCST Vs affective temperament in cases

			CT	DT	IT	HT	AT
Spearman's rho	STROOP TEST	Correlation Coefficient	-.287	-.003	.045	-.397*	.097
		Sig. (2-tailed)	.124	.988	.813	.030	.612
	WCST ERRORS	Correlation Coefficient	.078	-.188	.152	-.114	.058
		Sig. (2-tailed)	.684	.319	.422	.549	.761
	WCST PERCENT ERRORS	Correlation Coefficient	.023	-.141	.097	-.138	.012
		Sig. (2-tailed)	.904	.458	.611	.466	.951
	PERCEVERATIVE RESPONSE	Correlation Coefficient	.120	-.001	.107	-.028	.035
		Sig. (2-tailed)	.528	.996	.572	.884	.855
	PERCENT PERSEVERATIVE RESPONSE	Correlation Coefficient	.139	.144	.068	-.020	-.023
		Sig. (2-tailed)	.465	.448	.720	.918	.903

*p <0.05 **p <0.01

CT – Cyclothymic Temperament ; DT – Depressive Temperament ; IT – Irritable Temperament ; HT – Hyperthymic Temperament ; AT – Anxious Temperament

Table 16 : WCST Vs affective temperament in cases

			CT	DT	IT	HT	AT
Spearman's rho	PESEVERATIVE ERRORS	Correlation Coefficient	.105	-.056	.068	-.022	.066
		Sig. (2-tailed)	.581	.770	.721	.909	.730
	PERCENT PERSEVERATIVE ERRORS	Correlation Coefficient	.101	.101	.021	-.037	.043
		Sig. (2-tailed)	.595	.596	.912	.847	.823
	NON PERCEVERATIVE ERRORS	Correlation Coefficient	.224	-.310	.277	-.197	.070
		Sig. (2-tailed)	.233	.096	.138	.296	.715
	PERCENT NON PERSEVERATIVE ERRORS	Correlation Coefficient	.145	-.316	.229	-.152	.139
		Sig. (2-tailed)	.444	.089	.223	.424	.463

*p <0.05 **p <0.01

CT – Cyclothymic Temperament ; DT – Depressive Temperament ; IT – Irritable Temperament ; HT – Hyperthymic Temperament ; AT – Anxious Temperament

From the above table 16, no correlation was found between the Wisconsin card sorting test scores of perseverative errors, percent perseverative errors, non perseverative errors, percent non perseverative errors.

Table 17 : WCST Vs affective temperament in cases

			CT	DT	IT	HT	AT
Spearman's rho	CONCEPTUAL LEVEL RESPONSE	Correlation Coefficient	-.036	-.061	.064	-.081	.046
		Sig. (2-tailed)	.851	.750	.737	.671	.808
	PERCENT CONCEPTUAL LEVEL RESPONSE	Correlation Coefficient	.062	-.185	.065	-.081	.000
		Sig. (2-tailed)	.747	.328	.735	.670	1.000
	CATEGORIES COMPLETED	Correlation Coefficient	-.032	-.093	.027	-.092	.008
		Sig. (2-tailed)	.866	.627	.888	.628	.967

*p <0.05 **p <0.01

CT – Cyclothymic Temperament ; DT – Depressive Temperament ; IT – Irritable Temperament ; HT – Hyperthymic Temperament ; AT – Anxious Temperament

Table 17 also shows that there is no significant correlation between the scores conceptual level response, percent conceptual level response, number of categories completed with any of the temperament.

On the whole no significant correlation was made out between the performance of Wisconsin card test with the affective temperament scores.

Table 18 : working memory, TMT B in cases Vs clinical characteristics of bipolar probands

			ONSET AGE	DURATION OF ILLNESS	NO. MANIC EPISODES	NO. DEPRESSIVE EPISODES	NO. MIXED EPISODES
Spearman's rho	VERBAL WM N BACK1	Correlation Coefficient	.128	-.027	-.032	-.171	-.040
		Sig. (2-tailed)	.499	.888	.868	.365	.833
	VERBAL WM N BACK 2	Correlation Coefficient	.262	.183	-.034	.157	.169
		Sig. (2-tailed)	.162	.332	.860	.408	.373
	VISUAL WM N BACK 1	Correlation Coefficient	-.011	-.181	-.364*	.026	.311
		Sig. (2-tailed)	.955	.340	.048	.890	.094
	TMT B	Correlation Coefficient	-.086	.041	.093	-.196	-.027
		Sig. (2-tailed)	.653	.829	.624	.299	.888

*p <0.05 **p <0.01

The spearman's correlation shows significant correlation between visual N back 1 test scores and the number manic episodes in their first-degree relative patients with bipolar I disorder.

No significant correlation was found between verbal working memory and Trail making B tests and the illness characteristics of their first-degree relatives with bipolar I disorder. (table 18 and 19)

Table 19 : working memory, TMT B in cases Vs clinical characteristics of bipolar probands

			ILLNESS SEVERITY	PSYCHOTC SYMPTOM	NO OF HOSPITALISATIONS	NO OF SUICIDE ATTEMPTS	SUBSTANCE USE
Spearman's rho	VERBAL WM N BACK1	Correlation Coefficient	.071	-.338	-.306	-.154	-.091
		Sig. (2-tailed)	.710	.068	.100	.415	.634
	VERBAL WM N BACK 2	Correlation Coefficient	.243	-.032	-.057	.237	-.027
		Sig. (2-tailed)	.196	.868	.765	.206	.889
	VISUAL WM N BACK 1	Correlation Coefficient	-.148	-.157	-.207	.212	-.018
		Sig. (2-tailed)	.434	.407	.272	.260	.926
	TMT B	Correlation Coefficient	.012	-.216	-.148	-.012	-.052
		Sig. (2-tailed)	.951	.251	.435	.951	.784

*p <0.05 **p <0.01

Table 20 : Stroop test, WCST in cases Vs clinical characteristics of bipolar probands

			ONSET AGE	DURATION OF ILLNESS	NO. MANIC EPISODES	NO. DEPRESSIVE EPISODES	NO. MIXED EPISODES
Spearman's rho	STROOP TEST	Correlation Coefficient	-.241	.192	.102	.161	-.169
		Sig. (2-tailed)	.199	.309	.591	.395	.373
	WCST ERRORS	Correlation Coefficient	.479**	.241	.286	.298	.145
		Sig. (2-tailed)	.007	.200	.126	.110	.446
	WCST PERCENT ERRORS	Correlation Coefficient	.460*	.208	.263	.303	.065
		Sig. (2-tailed)	.011	.271	.160	.104	.734
	PERCEVERATIVE RESPONSE	Correlation Coefficient	.331	.116	.184	.203	.139
		Sig. (2-tailed)	.074	.541	.330	.283	.463
	PERCENT PERSEVERATIVE RESPONSE	Correlation Coefficient	.254	-.040	.010	.108	.151
		Sig. (2-tailed)	.176	.833	.958	.570	.424

*p <0.05 **p <0.01

There was significant correlation between the Wisconsin card sorting test total number of errors with the age of onset of bipolar illness and the number of suicidal attempts in the related patients.

The age of onset of bipolar disorder in the first-degree relatives of the study group is also positively correlated with the percent errors score of

Wisconsin card sorting test. No correlation was found for Stroop test with illness characteristics. (table 20 and 21)

Table 21 : Stroop test, WCST in cases Vs clinical characteristics of bipolar probands

			ILLNESS SEVERITY	PSYCHOTIC SYMPTOMS	NO OF HOSPITALI SATIONS	NO OF SUICIDE ATTEMPTS	SUBSTAN CE USE
Spearman's rho	STROOP TEST	Correlation Coefficient	.160	.162	.008	.035	.296
		Sig. (2-tailed)	.398	.392	.965	.854	.112
	WCST ERRORS	Correlation Coefficient	.189	-.108	.057	.368*	.118
		Sig. (2-tailed)	.318	.569	.764	.045	.536
	WCST PERCENT ERRORS	Correlation Coefficient	.142	-.101	.095	.239	-.009
		Sig. (2-tailed)	.453	.597	.618	.203	.964
	PERCEVERATIVE RESPONSE	Correlation Coefficient	.079	-.286	-.026	.297	.061
		Sig. (2-tailed)	.677	.126	.890	.111	.749
	PERCENT PERSEVERATIVE RESPONSE	Correlation Coefficient	-.058	-.255	-.097	.194	-.087
		Sig. (2-tailed)	.761	.174	.609	.304	.647

*p <0.05 **p <0.01

Table 22 : WCST in cases Vs clinical characteristics of bipolar probands

			ONSET AGE	DURATION OF ILLNESS	NO. MANIC EPISODES	NO. DEPRESSIVE EPISODES	NO. MIXED EPISODES
Spearman's rho	PESEVERATIVE ERRORS	Correlation Coefficient	.371*	.137	.211	.179	.141
		Sig. (2-tailed)	.044	.469	.264	.344	.458
	PERCENT PERSEVERATIVE ERRORS	Correlation Coefficient	.280	-.013	.069	.106	.109
		Sig. (2-tailed)	.134	.946	.719	.578	.568
	NON PERCEVERATIVE ERRORS	Correlation Coefficient	.383*	.216	.278	.261	.144
		Sig. (2-tailed)	.037	.252	.137	.164	.447
	PERCENT NON PERSEVERATIVE ERRORS	Correlation Coefficient	.318	.218	.322	.260	-.008
		Sig. (2-tailed)	.087	.248	.082	.165	.966

*p <0.05 **p <0.01

Table 22 and 23 shows positive correlation between the age of onset of bipolar illness in the related patients and the scores of perseverative errors and non perseverative errors.

No significant correlation was found for scores of percent perseverative errors and percent non perseverative errors.

Table 23 : WCST in cases Vs clinical characteristics of bipolar probands

			ILLNESS SEVERITY	PSYCHOTIC SYMPTOMS	NO OF HOSPITALISATIONS	NO OF SUICIDE ATTEMPTS	SUBSTANCE USE
Spearman's rho	PESEVERATIVE ERRORS	Correlation Coefficient	.078	-.263	-.037	.328	.035
		Sig. (2-tailed)	.683	.160	.848	.076	.855
	PERCENT PERSEVERATIVE ERRORS	Correlation Coefficient	-.056	-.217	-.128	.241	-.044
		Sig. (2-tailed)	.768	.250	.500	.199	.819
	NON PERCEVERATIVE ERRORS	Correlation Coefficient	.156	.008	.078	.303	.039
		Sig. (2-tailed)	.411	.968	.684	.104	.837
	PERCENT NON PERSEVERATIVE ERRORS	Correlation Coefficient	.128	.100	.090	.158	.026
		Sig. (2-tailed)	.501	.597	.638	.405	.891

*p <0.05 **p <0.01

Table 24 : WCST in cases Vs clinical characteristics of bipolar probands

			ONSET AGE	DURATION OF ILLNESS	NO. MANIC EPISODES	NO. DEPRESSIVE EPISODES	NO. MIXED EPISODES
Spearman's rho	CONCEPTUAL LEVEL RESPONSE	Correlation Coefficient	.379*	.269	.284	.246	-.096
		Sig. (2-tailed)	.039	.150	.129	.191	.613
	PERCENT CONCEPTUAL LEVEL RESPONSE	Correlation Coefficient	.463**	.266	.241	.224	.025
		Sig. (2-tailed)	.010	.156	.200	.234	.896
	CATEGORIES COMPLETED	Correlation Coefficient	.321	.212	.261	.229	-.060
		Sig. (2-tailed)	.084	.261	.163	.223	.752

*p <0.05 **p <0.01

The final scores of conceptual level response and percent conceptual level response is significantly positively correlated with the age of onset of bipolar illness in the probands.

No correlation was found between the number of categories completed and the clinical characteristics of bipolar disorder patients. (table 24 and 25)

Table 25 : WCST in cases Vs clinical characteristics of bipolar probands

			ILLNESS SEVERITY	PSYCHOTIC SYMPTOMS	NO OF HOSPITALISATIONS	NO OF SUICIDE ATTEMPTS	SUBSTANCE USE
Spearman's rho	CONCEPTUAL LEVEL RESPONSE	Correlation Coefficient	.227	.023	.130	.053	-.087
		Sig. (2-tailed)	.228	.903	.492	.781	.647
	PERCENT CONCEPTUAL LEVEL RESPONSE	Correlation Coefficient	.244	-.255	.094	.206	-.065
		Sig. (2-tailed)	.194	.174	.620	.274	.731
	CATEGORIES COMPLETED	Correlation Coefficient	.159	.016	.101	-.057	-.098
		Sig. (2-tailed)	.402	.934	.594	.766	.606

*p <0.05 **p <0.01

Table 26 : affective temperament in cases Vs clinical characteristics of bipolar probands

			ONSET AGE	DURATION OF ILLNESS	NO. MANIC EPISODES	NO. DEPRESSIVE EPISODES	NO. MIXED EPISODES
Spearman's rho	CYCLOTHYMIC TEMP	Correlation Coefficient	.181	-.068	-.190	-.073	.176
		Sig. (2-tailed)	.339	.720	.313	.700	.352
	DEPRESSIVE TEMP	Correlation Coefficient	-.323	-.141	-.163	.154	-.085
		Sig. (2-tailed)	.082	.456	.390	.418	.656
	IRRITABLE TEMP	Correlation Coefficient	.036	.137	-.135	.142	.297
		Sig. (2-tailed)	.849	.471	.478	.453	.111
	HYPERTHYMIC TEMP	Correlation Coefficient	-.016	.035	-.013	-.321	-.082
		Sig. (2-tailed)	.934	.856	.947	.083	.667
	ANXIOUS TEMP	Correlation Coefficient	-.004	.039	-.096	.035	-.177
		Sig. (2-tailed)	.984	.839	.615	.852	.351

*p <0.05 **p <0.01

Table 27 : affective temperament in cases Vs clinical characteristics of bipolar probands

			ILLNESS SEVERITY	PSYCHOTIS SYMPTOMS	NO OF HOSPITALISATIONS	NO OF SUICIDE ATTEMPTS	SUBSTANCE USE
Spearman's rho	CYCLOTHYMIC TEMP	Correlation Coefficient	-.009	-.230	-.147	.260	-.179
		Sig. (2-tailed)	.964	.221	.438	.165	.344
	DEPRESSIVE TEMP	Correlation Coefficient	-.298	.105	-.101	-.003	.035
		Sig. (2-tailed)	.110	.580	.594	.989	.856
	IRRITABLE TEMP	Correlation Coefficient	.137	.129	-.043	.408*	.136
		Sig. (2-tailed)	.471	.497	.820	.025	.473
	HYPERTHYMIC TEMP	Correlation Coefficient	.247	-.031	-.129	-.117	-.009
		Sig. (2-tailed)	.187	.870	.496	.537	.963
	ANXIOUS TEMP	Correlation Coefficient	.028	.286	-.313	.072	.262
		Sig. (2-tailed)	.885	.126	.093	.706	.162

*p <0.05 **p <0.01

Tables 26 and 27 in the previous pages assess the correlation between affective temperament of the study (cases) group and the illness characteristics of their related bipolar disorder patients.

Positive correlation was obtained for irritable temperament in the cases and the number of suicidal attempts in the bipolar patients.

No significant correlation was obtained for other temperament subscales of cyclothymic, depressive, hyperthymic and anxious temperaments with any of the illness characteristics.

DISCUSSION

Cognitive disturbances in bipolar disorder are well established. Recent research has been concentrating in studying the presence of such cognitive disturbances in the unaffected family members of bipolar patients. Studies also show that certain temperaments are predominant in bipolar disorder patients as well their unaffected family members.

This study aimed at assessing the presence of neurocognitive deficits and affective temperament in first-degree relatives of bipolar I disorder patients, comparing with healthy unrelated controls. This is chosen as, one of the criteria for establishing an endophenotype, the marker found in the affected family members must be present in unaffected family members at a higher rate than in the general population. The other criteria namely its association with the illness, its heritable nature, being a trait marker are established in many studies except its co-segregation with illness within families.

Structural clinical interview was used to select bipolar disorder probands. Their first-degree relatives were chosen applying strict selection criteria. Age group of 18-50 years was taken mainly to avoid any age related cognitive deficits. Formal education of at least 8^{th} standard was applied so that the subjects could understand the tests and perform. Subjects with IQ >70 (more than 25^{th} percentile in Raven's progressive matrices) were chosen for the study.

Similar criteria were applied for selection of control group and both groups were administered structured clinical interview to exclude the presence of any psychiatric illness. Subjects with history of any neurological illness or substance dependence were excluded to remove any confounding effects. The socio-demographic data of the study and control groups were matched with respect to age, sex, education and occupation.

The neuropsychological tests administered were from the National Institute of Mental Health And Neurosciences neuropsychology battery, 2004 which is a standardized test battery. The cognitive domains tested in this study are verbal and visual working memory, and executive function. N back 1 and 2 for verbal working memory, N back 1 for visual working memory; trail making test B, Stroop test and Wisconsin card sorting test for executive functioning.

On analysis of test performance of verbal working memory, the study group had poor performance compared to the controls, making more number of errors. The statistical test applied to compare two groups showed significant difference, concluding the verbal memory deficit in the first-degree relatives of bipolar patients compared to normal population. Similar deficit in verbal working memory were demonstrated by Kulkarni et al. (2010), Arts et al. (2008), Bora et al. (2007); but this study results were in discordance with few studies which showed no impairment verbal working memory in unaffected biological relatives of bipolar disorder

patients. (Bora et al. 2009, Keri et al. 2001, Clark et al. 2005, Kreman et al. 1998, Ferrier et al. 2004, Frantom et al. 2008, Antila et al. 2006)

Similar results were obtained N back 1 test for visual working memory in this study that the study group had more number of errors compared to controls and that the difference in their performance was statistically significant which is in concordance with studies by Ferrier et al. 2004 and Antila et al. 2006, but differing with the results of Trivedi et al. 2008 and Frantom et al. 2008 who showed no significant difference in test of visual working memory in unaffected biological relatives of bipolar probands compared to normal controls.

In test of executive functioning, trail making test B was administered. In this the study group took longer time to complete the trail than controls. This longer time includes time taken to make corrections whenever they made error in connecting the numbers and alphabets. The test scores showed significant difference comparing with controls, thus showing the unaffected family members of bipolar probands had impairment in set-shifting ability. (Similar results by Antila et al. 2008, Pattanayak et al. 2012, Arts et al. 2008)

The next test administered for executive function analysis is the Stroop test. The study group demonstrated statistically significant difference in their performance compared to normal controls. Though the time factor was taken for calculation of Stroop effect, study group made

more number of errors in reading each card when compared to control group. Since Stroop test is a standard test for assessing the response inhibition ability of a person, this study finding shows that unaffected first-degree relatives of bipolar patients had deficits in response inhibition. This study finding is proven by previous studies by Arts et al. 2008, Zalla et al. 2004, Bora et al. 2007, Frangou et al. 2005. Bora et al. in his meta-analysis concluded that response inhibition deficits as most consistent marker for endophenotype in bipolar disorder. But this finding is differed from those by Sobczak et al. 2002, Ferrier et al. 2004, Pattanayak et al. 2012 who showed there was no difference in performance of Stroop test in unaffected family members of bipolar probands and normal controls.

Study group scores on all parameters of Wisconsin card sorting test showed statistically significant differences when compared to controls. WCST is the gold standard test for measuring the executive functioning in the areas of concept formation, abstract reasoning and the ability to shift cognitive strategies in response to changing environments. The total number of errors was more for the study group and of this perseverative errors were especially more in that group compared to the control group, indicating set-shifting difficulties. The conceptual level response and the total number of categories completed were low in the study group indicating a poor concept formation capacity when compared to normal controls. Similar results of executive dysfunction in set-shifting, abstract

reasoning and concept formation were given by Trivedi et al. 2008, Bora et al. 2007, Frantom et al. 2008, Clark et al. 2005. Few studies (Frangou et al. 2005, Keri et al. 2001, Kreman et al. 1998) concluded no significant impairment in WCST test performance in healthy biological relatives of bipolar patients.

For assessing the affective temperament in the unaffected family members of bipolar probands, the TEMPS-A short version was used which is validated scale for assessment of temperament. The score were higher for cyclothymic (similar findings Leonhard et al. 1962, Winokur et al. 1969, Weissman et al. 1984, Klein et al. 1986, Maier et al. 1995, Chiaroni et al. 2005, Mendlowicz et al. 2005), hyperthymic (Weissman et al. 1984, Hoffman et al. 1921, Mendlowicz et al. 2005) and anxious temperament (Mendlowicz et al. 2005) in the study group. There was statistically significant difference in these temperament subscales between the study and control groups, showing the predominant presence of cyclothymic, hyperthymic and anxious temperament in unaffected first-degree relatives of bipolar patients.

When attempted to find the correlation between the neuropsychological test performances and the affective temperament, few correlations were established in this study. Performances of verbal N back 1 for working memory had significant correlation with the depressive temperament. Presence of cyclothymic, irritable and anxious temperament

had positive correlation with the performance of verbal N back 2 test for working memory.

Also visual working memory scores of N back 1 test had significant correlation with the presence of cyclothymic temperament. Whereas the Stroop test scores had significant negative correlation with the hyperthymic temperament.

None of the Wisconsin card sorting test scores showed any correlation with the affective temperament scores in this study.

The final measure was to find any correlation with the neuropsychological tests and affective temperament of the study group with the illness characteristics of their related bipolar disorder patients.

There was significant correlation in the performance of visual N back test and the number of manic episodes in the bipolar probands.

The Wisconsin card sorting test total number of errors and the percent errors scores of the study group had statistically significant correlation with the age of onset of bipolar disorder in probands; in addition WCST errors showed significant correlation with the number of suicide attempts in their bipolar probands.

Similarly positive correlation was shown between the age of onset of illness in the bipolar probands and the WCST test scores of perseverative errors, non-perseverative errors, conceptual level response and the percent conceptual level response.

On analysis of correlation between affective temperament and the illness characteristics of bipolar probands, only the presence of irritable temperament in the unaffected first-degree relatives had significant positive correlation with the number suicide attempts in their related bipolar probands.

From practical point of view cognitive functions have important implications in day to day life and contribute to the social and occupational performance of the individual. Disturbance in these cognitive functions may pose problems in coping with daily life tasks.

From this study it is established that cognitive impairment in working memory and executive functioning and, the cyclothymic, hyperthymic and anxious temperaments could be possible endophenotype markers of bipolar disorder. Establishing these markers may aid in early identification of the illness and to provide early intervention strategies, so that the overall severity and burden of bipolar illness could be reduced. As endophenotypes, these cognitive and temperamental markers may help in identifying the underlying neurobiological mechanisms and the pathogenesis of bipolar disorder. Thus establishing an etiological diagnosis rather than diagnosing only from clinical presentations which are widely varied.

CONCLUSION

1. The first-degree relatives of patients with bipolar disorder displayed significant impairment in all the neurocognitive tests when compared to controls.
2. The first-degree relatives showed significant cyclothymic, hyperthymic and anxious temperament when compared to controls.
3. The test of verbal working memory N back 1 correlated significantly with depressive temperament in first-degree relatives of bipolar probands.
4. The test of verbal working memory N back 2 correlated significantly with cyclothymic, irritable and anxious temperament in first-degree relatives of bipolar probands.
5. The test of visual working memory N back 1 correlated significantly with cyclothymic temperament in first-degree relatives of bipolar probands.
6. Stroop test correlated significantly with hyperthymic temperament in first-degree relatives of bipolar probands.
7. The test of visual working memory N back 1 in first-degree relatives of bipolar probands correlated significantly with the number of manic episodes in bipolar probands.
8. The Wisconsin card sorting test scores of total number of errors, percent errors, perseverative errors, non-perseverative errors,

conceptual level response and the percent conceptual level response in first-degree relatives of bipolar patients significantly correlated with the age of onset of illness in bipolar probands.

9. The WCST total number of errors in first-degree relatives of bipolar patients significantly correlated with the number of suicide attempts in bipolar probands.

10. The irritable temperament in first-degree relatives of bipolar patients significantly correlated with the number suicide attempts in their related bipolar probands.

LIMITATIONS

- The study sample size in both cases and controls groups is low which might reduce the power of study.
- This is a cross sectional study assessing the cognitive functioning which might bring about individual variations during one assessment.
- The scale used for assessment of affective temperament is not available in local language. It was translated from English to local language by a translator, back translated to English and compared with the original scale. But the scale was not standardized to local population.

FUTURE DIRECTIONS

- The future scope of my study is a longitudinal study, assessing the neurocognitive functioning of first-degree relatives of bipolar probands for a period of at least 6-12 months follow up, to remove individual variations in one assessment alone.
- Also to employ cognitive remediation practices to both bipolar probands and their unaffected first-degree relatives and assess the impact of such practices on the cognitive performances during follow up.
- In future studies the inter group differences in cognitive performance and affective temperament among parents, siblings and children of bipolar probands could be studied to determine the severity of impairment in each group.
- In future this study could be extended to include patients with various bipolar spectrum disorders and their first-degree relatives to assess specific domains of cognitive impairment in each disorder groups.

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APPENDIX 1

PROFORMA

1. Name :

2. Age

3. Sex :

4. Occupation :

5. Marital status : Married / Unmarried

6. Domicile : Rural / Urban

7. Educational status: Primary / secondary / degree

8. Socio economic status: low / middle / high

9. Religion : Hinduism / Christianity / Islam

10. Relation to patient :

APPENDIX 2

PROFORMA-CLINICAL CHARACTERISTICS OF BIPOLAR I DISORDER PATIENTS

1.Name :

2.Age of onset of illness :

3.Duration of illness :

4.No. of manic episodes :

5.No. of depressive episodes :

6.No. of mixed episodes :

7.Severity of illness [duration of illness/ total no. of episodes] :

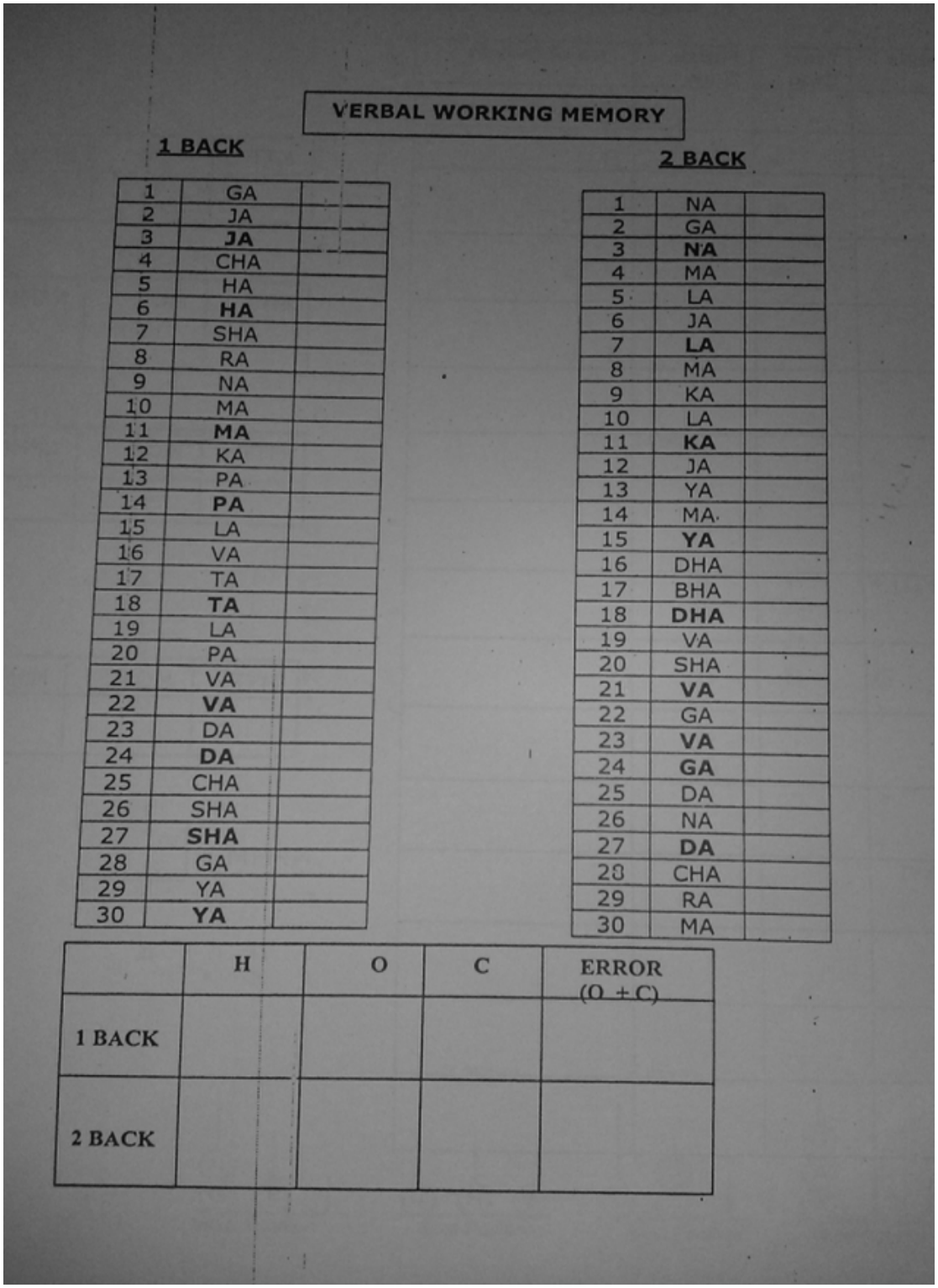
8.Presence of psychotic features in any episode :

9.No. of hospitalizations :

10.No. of suicidal attempts :

11.Presence of co morbid substance use :

APPENDIX 3



VERBAL WORKING MEMORY

1 BACK

1	GA	
2	JA	
3	**JA**	
4	CHA	
5	HA	
6	**HA**	
7	SHA	
8	RA	
9	NA	
10	MA	
11	**MA**	
12	KA	
13	PA	
14	**PA**	
15	LA	
16	VA	
17	TA	
18	**TA**	
19	LA	
20	PA	
21	VA	
22	**VA**	
23	DA	
24	**DA**	
25	CHA	
26	SHA	
27	**SHA**	
28	GA	
29	YA	
30	**YA**	

2 BACK

1	NA	
2	GA	
3	**NA**	
4	MA	
5	LA	
6	JA	
7	**LA**	
8	MA	
9	KA	
10	LA	
11	**KA**	
12	JA	
13	YA	
14	MA	
15	**YA**	
16	DHA	
17	BHA	
18	**DHA**	
19	VA	
20	SHA	
21	**VA**	
22	GA	
23	**VA**	
24	**GA**	
25	DA	
26	NA	
27	**DA**	
28	CHA	
29	RA	
30	MA	

	H	O	C	ERROR (O + C)
1 BACK				
2 BACK				

APPENDIX 4

VISUAL WORKING MEMORY

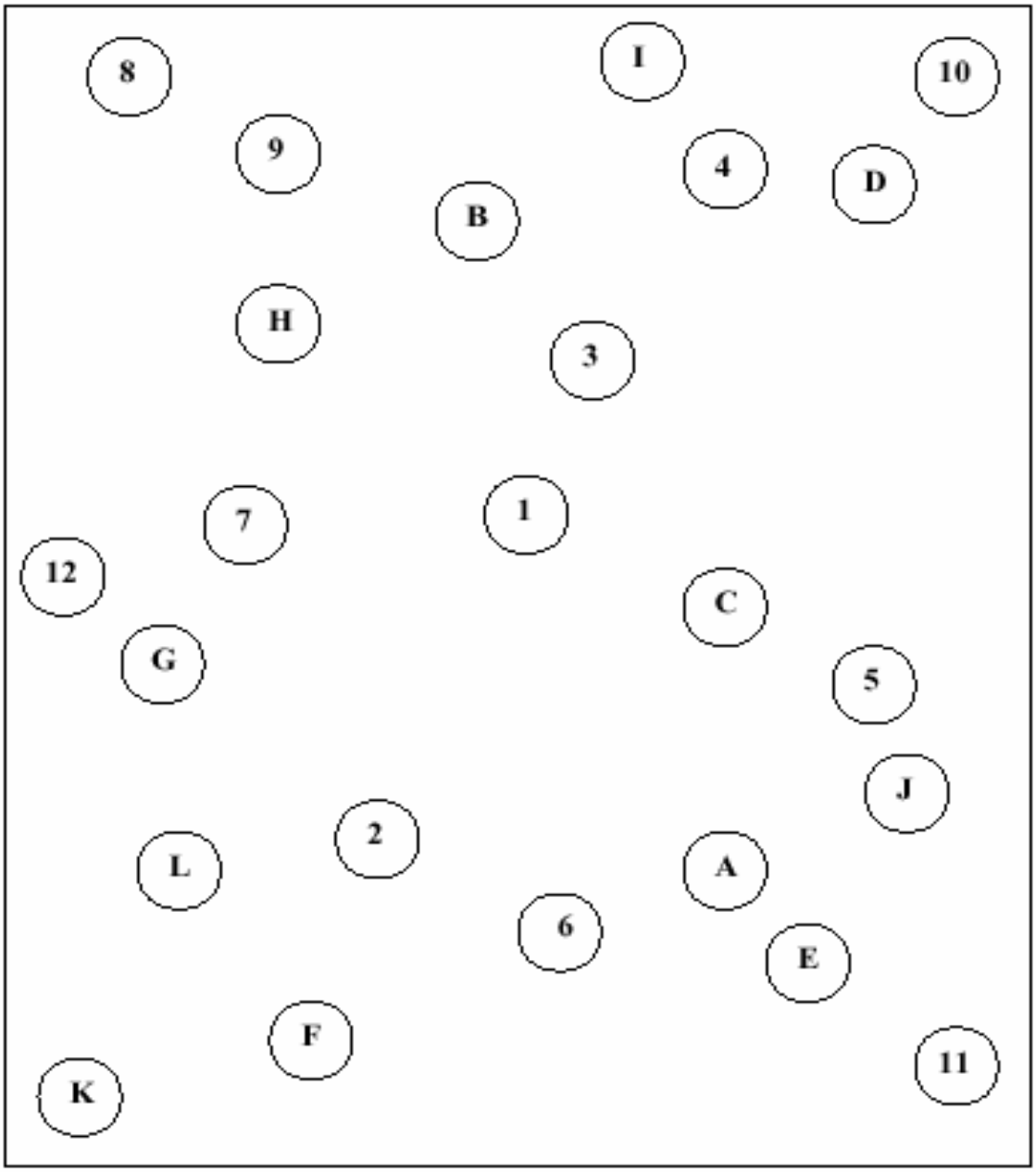
NAME:

	H	O	C	ERROR O+C
1 BACK				

APPENDIX 5

TRAIL MAKING TEST B

TIME:



APPENDIX 6

STROOP COLOUR TEST

SCORING

NAME:

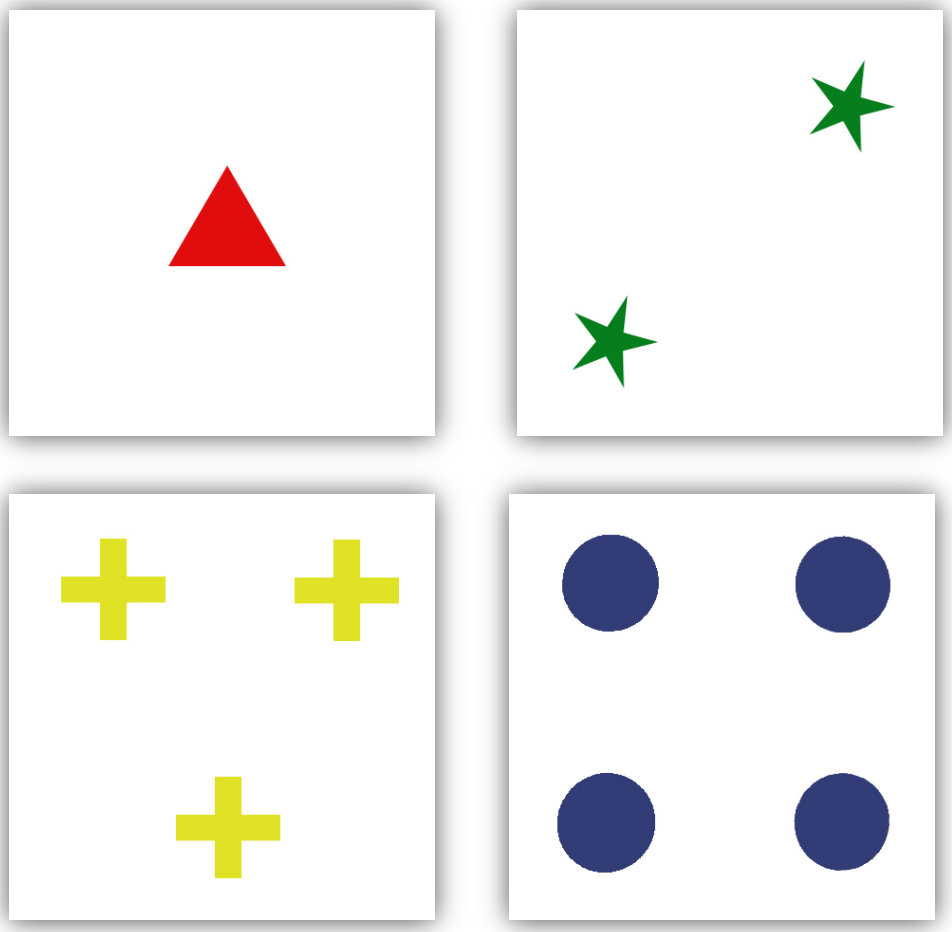
CARD	NO. OF ERRORS	TIME TAKEN(t)
CARD I		
CARD II		
CARD III		

Stroop effect = t III – (t I + t II / 2)

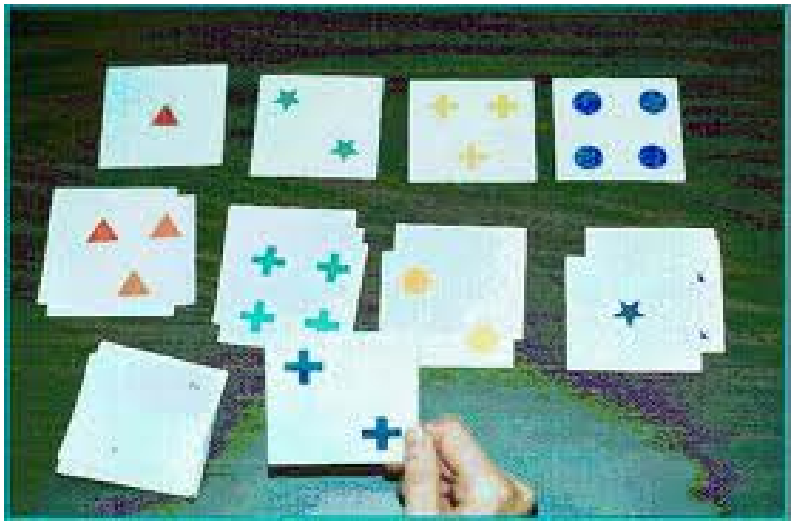
APPENDIX 7

WISCONSIN CARD SORTING TEST

STIMULUS CARDS



CARD SORTING



WCST SCORING SHEET

SCORING AREA

	Raw score	Standard score	*T* score	Percentile score
Number of Trials Administered				
Total Number Correct				
Total Number of Errors				
Percent Errors				
Perseverative Responses				
Percent Perseverative Responses				
Perseverative Errors				
Percent Perseverative Errors				
Nonperseverative Errors				
Percent Nonperseverative Errors				
Conceptual Level Responses				
Percent Conceptual Level Responses				

APPENDIX 8

TEMPS-A, a short version

1. My ability to think varies greatly from sharp to dull for no apparent reason.
2. I constantly switch between being lively and sluggish.
3. I get sudden shifts in mood and energy.
4. The way I see things is sometimes vivid, but at other times lifeless.
5. My mood often changes for no reason.
6. I go back and forth between being outgoing and being withdrawn from others.
7. My moods and energy are either high or low, rarely in between.
8. I go back and forth between feeling overconfident and feeling unsure of myself.
9. My need for sleep varies a lot from just a few hours to more than 9 h.
10. I sometimes go to bed feeling great, and wake up in the morning feeling life is not worth living.
11. I can really like someone a lot, and then completely lose interest in them.
12. I am the kind of person who can be sad and happy at the same time.
13. People tell me I am unable to see the lighter side of things.
14. I'm the kind of person who doubts everything.
15. I am a very skeptical person.
16. I am by nature a dissatisfied person.
17. I'm a sad, unhappy person.
18. I think things often turn out for the worst.
19. I give up easily.
20. I complain a lot.
21. People tell me I blow up out of nowhere.
22. I can get so furious I could hurt someone.
23. I often get so mad that I will just trash everything.
24. When crossed, I could get into a fight.

25. When I disagree with someone, I can get into a heated argument.

26. When angry, I snap at people. 27. I am known to swear a lot.

28. I have been told that I become violent with just a few drinks.

29. I have a gift for speech, convincing and inspiring to others.

30. I often get many great ideas.

31. I love to tackle new projects, even if risky.

32. I like telling jokes, people tell me I'm humorous.

33. I have abilities and expertise in many fields.

34. I am totally comfortable even with people I hardly know.

35. I love to be with a lot of people.

36. I am the kind of person who likes to be the boss.

37. I am often fearful of someone in my family coming down with a serious disease.

38. I'm always thinking someone might break bad news to me about a family member.

39. When someone is late coming home, I fear they may have had an accident.

Answer ‘yes’ or ‘no’ suitably

TAMIL TRANSLATION OF TEMPS-A SHORT VERSION

1. என் சிந்தனை திறன், எந்தக்காரணமும் இல்லாமல் கூர்மையானதிலிருந்து மந்தமானதாக பெருமளவில் வேறுபடுகிறது.
2. நன் உற்சாக மூட்டுவதாக இருப்பது மற்றும் மந்தமாக இருப்பது. இவற்றில் தொடர்ந்து மாறுபடுகிறேன்.
3. என் மனநிலை மற்றும் ஆற்றல் திடீர் மாற்றங்கள் பெறுகின்றன.
4. என்னுடைய கண்ணோட்டம் சில நேரங்களில் தெளிவாகவும், மற்ற நேரங்களில் உயிரற்றதாகவும் உள்ளது.
5. என் மனநிலை அடிக்கடி காரணமில்லாமல் மாறுகிறது.
6. சில நேரங்களில் மற்றவர்களிடம் சகஜமாகவும், மற்ற நேரங்களில் ஒதுங்கியும் இருக்கிறேன்.
7. என் மனநிலை மற்றும் ஆற்றல் ஒன்று அதிக அளவில் அல்லது குறைந்த அளவில் உள்ளது. அரிதாக இவற்றிற்கிடையில் உள்ளது.
8. நான் அளவுக்கு மீறிய தன்னம்பிக்கை உடையவனாகவும் , தெளிவற்றவனாகவும், முன்னுக்குப்பின்னாகவும் மாறுகிறேன்.
9. என் தூக்கத்தின் தேவை, சில மணி நேரங்களிலிருந்து ஒன்பது மணி நேரத்திற்கும் மேலாக, பெருமளவில் வேறுபடுகிறது.
10. நான் சில சமயங்களில் மிகவும் உற்சாகமாகவும் உறக்கச் செல்கிறேன். ஆனால் காலையில் எழும்போது இந்த வாழ்க்கையை மதிப்பற்றதாக உணர்கிறேன்.
11. என்னால் உண்மையாகவே ஒருவரை மிகவும் நேசிக்க முடியும். பிறகு அவர்களிடம் ஈடுபாட்டை இழக்கிறேன்.

12. நான் எப்படிப்பட்ட நபர் என்றால் என்னால் ஒரே சமயத்தில் கவலையாகவும், மகிழ்ச்சியாகவும் இருக்கமுடியும்.

13. என்னால் ஒரு விஷயத்தில் இலகுவான பக்கத்தைப் பார்க்க முடிவதில்லை என்று மக்கள் கூறுகின்றனர்.

14. நான் எப்படிப்பட்ட நபர் என்றால், எல்லாவற்றையும் சந்தேகத்துடன் பார்ப்பவன்.

15. நான் மிகவும் நம்பிக்கை இல்லாத ஒரு நபர்.

16. நான் இயற்கையாகவே, ஒரு மனநிறைவு இல்லாத நபர்.

17. நான் ஒரு சோகமான, மகிழ்ச்சியற்ற ஆள்.

18. அடிக்கடி விஷயங்கள் மோசமானதாக மாறுவதாக நினைக்கிறேன்.

19. நான் எளிதில் முயற்சி செய்வதை விட்டு விடுகிறேன்.

20. நான் நிறை குறைகளைக் கூறுவேன்.

21. திடீரென அதிகப்படியான கோபத்தை மற்றவர்களிடம் காட்டுகிறேன்.

22. நான் ஒருவரைக் காயப்படுத்தும் அளவிற்குச் சீற்றம் அடைகிறேன்.

23. நான் அடிக்கடி எல்லாவற்றையும் சிதைக்குமளவிற்குக் கோபமடைகிறேன்.

24. என் வழியில் மற்றவர்கள் குறுக்கிடும்போது நான் சண்டையில் ஈடுபடுகிறேன்.

25. யாருடனாவது கருத்து வேறுபாடு ஏற்றபடும் போது நான் வாக்குவாதத்தில் ஈடுபடுகிறேன்.

26. நான் கோபம் கொள்ளும் போது மற்றவர்களிடம் கட்டுப்பாட்டை இழக்கிறேன்.

27. நான் நிறைய சத்தியம் செய்பவன்.

28. நான் கொஞ்சம் மது அருந்தினாலே மிகவும் வன்முறையாக மாறுகிறேன் என்று கூறக் கேள்விப்பட்டிருக்கிறேன்.

29. நான் என்னுடைய பேச்சு மற்றும் மற்றவர்களைத் திருப்திப் படுத்தும் எழுச்சியூட்டும் தன்மையைப் பெற்றவன்.

30. எனக்கு அடிக்கடி பல பெரிய யோசனைகள் தோன்றும்.

31. நான் புதிய திட்டங்களைச் சமாளிக்க விரும்புகிறேன், ஆபத்தானதாக இருந்தாலும் கூட.

32. நகைச்சுவைகள் செய்வதை நான் விரும்புகிறேன் மக்கள் என்னை வேடிக்கையானவன் என்று கூறுகின்றேனர்.

33. எனக்குப் பல துரைகளில் திறனும் நிபுணத்துவமும் உண்டு.

34. எனக்கு அரிதாகத் தெரிந்தவர்களுடன் கூட வசதியாக இருப்பேன்.

35. நிறையப் பேர்களுடன் இருப்பதை நான் விரும்புகிறேன்.

36. நான் தலைவனாய் இருப்பதை விரும்பும் ஒரு நபர்.

37. என் குடும்பத்தில் யாருக்காவது தீவிர நோயல், உடல்நலக்குறைவு ஏற்படும் என்று அடிக்கடி பயப்படுவேன்.

38. யாராவது என் குடும்பத்தினரைப் பற்றிய கெட்டச் செய்தியைக் தருவார்கள் என்று எப்போதும் யோசிப்போன்.

39. யாராவது வீடு திரும்பத் தாமதமானால் அவர்களுக்கு விபத்து ஏற்பட்டிருக்குமோ என்று பயப்படுவேன்.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. L. Thenmozhi
PG in MD Psychiatry
Madras Medical College ,Chennai -3

Dear Dr. L. Thenmozhi

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A comparative study on neurocognition and affective temperature in first-degree relatives of bipolar disorder patients" No.34072012.

The following members of Ethics Committee were present in the meeting held on 24.07.2012 conducted at Madras Medical College, Chennai -3.

1.	Dr. S.K. Rajan. M.D.,FRCP.,DSc	-- Chairperson
2.	Prof. Pregna B. Dolia MD Vice Prinicpal, Madras Medical College, Chennai-3 Director , Inst. of Biochemistry, MMC, Ch-3	--Member Secretary
3.	Prof. Kalaiselvi MD Prof of Pharmacology ,MMC, Ch-3	-- Member
4.	Prof. C. Rajendiran, MD Director , Inst. of Internal Medicine, MMC, Ch-3	-- Member
5.	Prof. MD Ali M.D,. D.M., Prof & HOD, Dept. of MGE, MMC, Ch-3	-- Member
6.	Prof. S. Deivanayagam MS Prof of Surgery, MMC, Ch-3	-- Member
7.	Thiru. S. Govindsamy. BABL	-- Lawyer
8.	Tmt. Arnold Soulina MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு :

பெயர் : தேதி :

வயது : உள் நோயாளி எண் :

பால் : ஆராய்ச்சி சேர்க்கை என் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

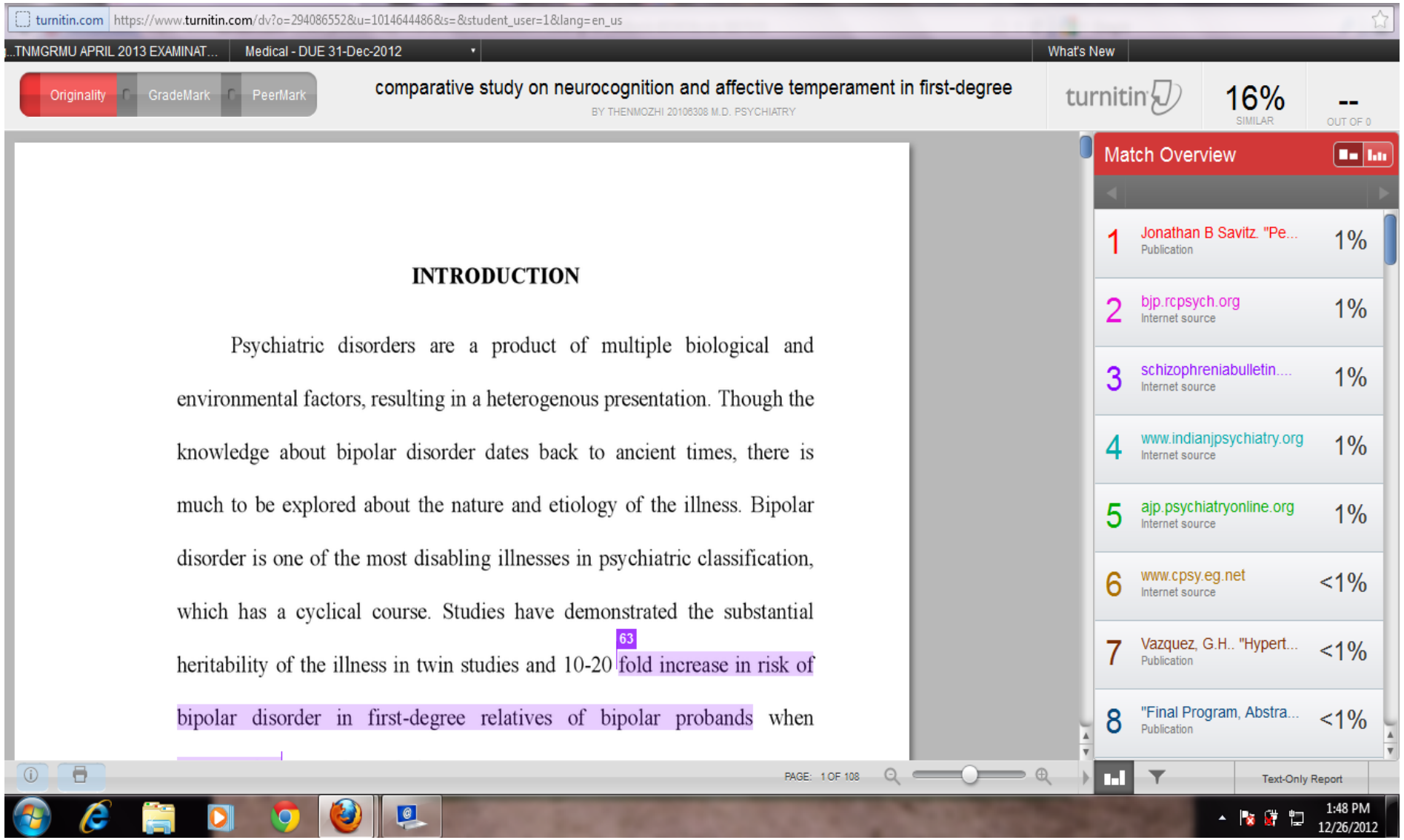
எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு நான் எனத சம்மதத்தைத் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்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INTRODUCTION
Psychiatric disorders are a product of multiple biological and environmental factors, resulting in a heterogenous presentation. Though the knowledge about bipolar disorder dates back to ancient times, there is much to be explored about the nature and etiology of the illness. Bipolar disorder is one of the most disabling illnesses in psychiatric classification, which has a cyclical course. Studies have demonstrated the substantial heritability of the illness in twin studies and 10-20 fold increase in risk of bipolar disorder in first-degree relatives of bipolar probands when
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